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January 20, 2004

VIA HAND DELIVERY

William T. Walsh
Clerk, United States District Court
Mitchell H. Cohen Bldg. & U.S. Courthouse
One John F. Gerry Plaza
Camden, New Jersey 08101

Re: SmithKline Beecham PLC, et al. v. Teva Pharmaceuticals Industries Ltd., et al.
Civil Action No.: To Be Assigned

Dear Mr. Walsh:

We are counsel for Plaintiffs SmithKline Beecham PLC, SB Pharmco Puerto Rico Inc. and Smithkline Beecham Corporation (collectively "Plaintiffs") in the above-referenced action. Enclosed for filing please find an original and five copies of Plaintiffs' (i) Complaint, (ii) the accompanying Summons for each defendant, (iii) a Civil Cover Sheet, and (iv) a Rule 7.1 Disclosure Statement. Kindly sign and "seal" each Summons, mark copies of the Complaint, Civil Cover Sheet, and Rule 7.1 Disclosure Statement "filed," and return same to me in the enclosed self-addressed FedEx envelope.

Also enclosed, pursuant to the District of New Jersey's filing fee, is a check for $150.00. Finally, note that pursuant to the new e-filing requirements of the District of New Jersey, enclosed is a CD ROM containing electronic versions of the foregoing documents.

Thank you for your attention to this matter.

Very truly yours,

Jason E. Halper

16212/2
01/20/04 1498776.01

Enclosures

cc: John W. Treece, Esq. (via FedEx w/encls.)
Jeffrey P. Kushan, Esq. (via FedEx w/encls.)

Douglas S. Eakeley (DE-7060)
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Attorneys for Plaintiffs

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SMITHKLINE BEECHAM PLC, an English Public Limited Company, SB PHARMCO PUERTO RICO INC., a Puerto Rican Corporation, and, SMITHKLINE BEECHAM CORPORATION, a Pennsylvania Corporation, Plaintiffs, v. TEVA PHARMACEUTICAL INDUSTRIES LTD., an Israeli Company, TEVA PHARMACEUTICALS USA, INC., a Delaware Corporation, Defendants.	Civil Action No. _____ **COMPLAINT**

In this patent infringement action, Plaintiffs SmithKline Beecham PLC, SB Pharmco Puerto Rico Inc. and SmithKline Beecham Corporation (collectively "Plaintiffs"), for their complaint against Defendants, Teva Pharmaceutical Industries Ltd. and Teva Pharmaceuticals USA, Inc., allege as follows:

PARTIES

1. Plaintiff SmithKline Beecham PLC is a public limited company organized under the laws of England and Wales with its principal place of business at 980 Great West Road, Brentford, Middlesex, TW89GS, England.

2. Plaintiff SB Pharmco Puerto Rico Inc. is a company organized and existing under the laws of Puerto Rico with its principal place of business at State Road No. 172, Km 9.1/Bo. Certenejas, Cidra, Puerto Rico, 00739.

3. Plaintiff SmithKline Beecham Corporation is a company organized and existing under the laws of the Commonwealth of Pennsylvania with its principal place of business at One Franklin Plaza, 200 North 16th Street, Philadelphia, Pennsylvania, 19102.

4. SmithKline Beecham Corporation maintains a regional sales office at 6000 Sagemore Drive, Suite 6201, Marlton, New Jersey, 08053.

5. On information and belief, Defendant Teva Pharmaceutical Industries Ltd. (referred to hereinafter as "Teva Ltd.") is a company organized and existing under the laws of Israel having its principal place of business at 5 Basel St. Petach Tikva 49131, Israel.

6. On information and belief, Defendant Teva Pharmaceuticals USA, Inc. (referred to hereinafter as "Teva USA") is a Delaware corporation having its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090.

7. On information and belief, Teva Ltd. owns 100% of the ownership and voting interest in Teva USA.

8. On information and belief, Teva USA is controlled and/or dominated by Teva Ltd.

9. On information and belief, Teva Ltd. conducts its operations, in part, through subsidiaries in Israel, Europe and North America, including Teva USA.

JURISDICTION AND VENUE

10. This is an action for patent infringement, arising under 35 U.S.C. § 1 et seq. generally, and 35 U.S.C. § 271(e)(2) specifically.

11. This Court has subject matter jurisdiction over this dispute pursuant to 28 U.S.C. §§ 1331 and 1338.

12. On information and belief, Teva USA is registered to do business in the State of New Jersey and maintains offices in, at least, Fairfield, New Jersey and Elmwood Park, New Jersey.

13. On information and belief, Teva Ltd. regularly transacts business within New Jersey, including but not limited to Teva Ltd.'s direction of the operations and management of Teva USA inclusive of Teva USA's New Jersey facilities, as well as shipping drugs to Teva USA from locations outside the United States for distribution by Teva USA within the United States generally and New Jersey specifically.

14. On information and belief, Teva USA acts as an agent of Teva Ltd. with respect to, at least, acts and conduct alleged in this complaint.

15. On information and belief, Teva Ltd. exercises substantially complete control over Teva USA with respect to, at least, the acts alleged in this complaint.

16. On information and belief, Teva Ltd. directed Teva USA to perform the acts alleged in this complaint to, in whole or in part, shield itself from liability for patent infringement based upon those acts.

17. This Court has personal jurisdiction over Teva USA because Teva USA resides in this judicial district and engages in continuous and systematic contacts with the State of New Jersey.

18. Teva USA's acts and contacts with the State of New Jersey, as an agent of Teva Ltd., are attributable to Teva Ltd. for jurisdictional purposes.

19. On information and belief, the degree of control exercised by Teva Ltd. over Teva USA, and/or the purposes for the exercise of that control, warrant piercing the

corporate veil of Teva USA and attributing Teva USA's relevant acts and contacts with the State of New Jersey to Teva Ltd.

20. This Court has personal jurisdiction over Teva Ltd. because Teva Ltd. maintains sufficient minimum contacts, both general and specific, with New Jersey (including but not necessarily limited to those described in paragraphs 12 through 19 above), and/or such sufficient minimum contacts are attributable to Teva Ltd., and the exercise of such jurisdiction is consistent with the requirements of due process and does not offend traditional notions of fair play and substantial justice.

21. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391 and 1400.

GENERAL ALLEGATIONS

22. On March 26, 1991, the United States Patent and Trademark Office issued U.S. Patent No. 5,002,953 ("the '953 Patent"). A true and correct copy of the '953 Patent is attached hereto as Exhibit A.

23. SmithKline Beecham Corporation is the current assignee of the '953 Patent.

24. SB Pharmco Puerto Rico Inc. is the sole entity licensed by SmithKline Beecham Corporation to, *inter alia*, sell the claimed invention of the '953 Patent in the United States.

25. SmithKline Beecham Corporation is the sole entity appointed by SB Pharmco Puerto Rico Inc. to distribute the drug covered by the United States Food and Drug Administration ("FDA")-approved New Drug Application ("NDA") No. 21-071 and marketed under the tradename Avandia®, the active ingredient of which is rosiglitazone maleate (hereinafter "Avandia®" or "the Avandia® drug product"), in the United States.

26. Pursuant to a license agreement for the '953 Patent, SB Pharmco Puerto Rico Inc. is obligated to pay royalties to SmithKline Beecham PLC on sales of Avandia® by SmithKline Beecham Corporation.

27. Plaintiffs own all rights, title and interest in the '953 Patent, including all rights needed to bring this action in Plaintiffs' names.

28. The '953 Patent is listed in the list of Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book"), maintained by the FDA, as a patent "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug" Avandia®. 21 U.S.C. § 355(b)(1).

29. On information and belief, through the coordinated efforts of research and development staff in Israel, Europe and North America, Teva Ltd. seeks to constantly expand the range of generic products sold by it.

30. On information and belief, Teva Ltd. actively reviews pharmaceutical patents and seeks opportunities to challenge those patents.

31. On information and belief, Teva Ltd. reviewed the '953 Patent and certain commercial and economic information relating to Avandia®, including estimates of the revenues generated by the sale of Avandia®, and decided to file an abbreviated new drug application ("ANDA"), seeking approval to market a generic copy of Avandia®.

32. On information and belief, Teva USA has filed an ANDA with the FDA seeking approval to market a generic copy of the Avandia® drug product.

33. On information and belief, after GSK had commenced in this Court Civil Action No. 03-4037 (FLW), Teva USA amended its ANDA to include a "Paragraph IV" certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the '953 Patent is invalid or will not be infringed by the manufacture, use, or sale of the generic copy of Avandia® covered

by Teva USA's ANDA. On information and belief, before the date such amendment was filed, Teva USA had included a certification in its ANDA that did not contest the validity, infringement or enforceability of the '953 patent.

34. On information and belief, Teva Ltd. made the ultimate decision, and encouraged and directed Teva USA, to file the above-described ANDA and "Paragraph IV" certification, and Teva USA did so at Teva Ltd.'s direction. On information and belief, Teva Ltd. was necessarily aware of the '953 Patent when it directed Teva USA to file the above-described ANDA with its original certifications, and with the new certifications subsequently filed in that ANDA. Unless otherwise indicated, Teva USA and Teva Ltd. shall hereinafter be referred to collectively as "Teva."

35. On or about December 10, 2003, Plaintiffs received a letter from Teva purporting to be the notice of Teva's ANDA containing a "Paragraph IV" certification required by 21 U.S.C. § 355(j)(2)(B)(i)-(ii).

36. Pursuant to 35 U.S.C. § 271(e)(2)(A), Teva's filing of an amended ANDA seeking marketing approval for its generic copy of the Avandia® drug product is an act of infringement of one or more claims of the '953 Patent entitling Plaintiffs to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an order of this Court that the effective date of approval for Teva's ANDA be a date which is not earlier than the expiration date of the '953 Patent, a date which is currently August 30, 2008.

37. On information and belief, Teva had no adequate good faith basis for filing the "Paragraph IV" certification accompanying and amending its ANDA.

COUNT ONE

(Direct Infringement of the '953 Patent Against Teva Ltd. and Teva USA)

38. Plaintiffs incorporate and reallege paragraphs 1 through 37 above, as if set forth in full herein.

39. Through the conduct alleged above, both Teva Ltd. and Teva USA (collectively "Teva") have directly infringed, and continue to infringe directly, one or more claims of the `953 Patent.

40. On information and belief, Teva's direct infringement of the `953 Patent has been willful.

41. By reason of Teva's direct infringement of the `953 Patent, Teva has caused and continues to cause Plaintiffs to suffer damage and irreparable harm. On information and belief, Teva's direct infringement of the `953 Patent will continue unless enjoined by this Court.

42. Plaintiffs have no adequate remedy at law for Teva's direct infringement of the `953 Patent.

43. This is an exceptional case within the meaning of 35 U.S.C. § 285, which warrants reimbursement of Plaintiffs' reasonable attorney fees.

COUNT TWO

(Inducement of Infringement of the '953 Patent Against Teva Ltd.)

44. Plaintiffs incorporate and reallege paragraphs 1 through 37 above, as if set forth in full herein.

45. Through the conduct alleged above, Teva Ltd. has knowingly and actively induced Teva USA to infringe, and continue to infringe, one or more claims of the `953 Patent.

46. On information and belief, Teva Ltd.'s inducement of Teva USA's direct infringement of the `953 Patent has been willful and intentional.

47. By reason of Teva Ltd.'s inducement of Teva USA's direct infringement of the `953 Patent, Teva Ltd. has caused and continues to cause Plaintiffs to suffer damage and irreparable harm. On information and belief, Teva Ltd.'s inducement of Teva USA's direct infringement of the `953 Patent will continue unless enjoined by this Court.

48. Plaintiffs have no adequate remedy at law for Teva Ltd.'s inducement of Teva USA's direct infringement of the `953 Patent.

49. This is an exceptional case within the meaning of 35 U.S.C. § 285, which warrants reimbursement of Plaintiffs' reasonable attorney fees.

RELIEF SOUGHT

WHEREFORE, Plaintiffs pray:

A. That judgment be entered that, pursuant to 35 U.S.C. § 271(e)(2)(A), both Teva Ltd. and Teva USA have directly infringed one or more claims of the '953 Patent;

B. That judgment be entered that the manufacture, use, sale or offer to sell within the United States, or importation into the United States of the generic copy of Avandia® described in Teva Ltd. and Teva USA's ANDA infringes one or more claims of the '953 Patent;

C. That judgment be entered that, pursuant to 35 U.S.C. § 271(b) and 35 U.S.C. § 271(e)(2)(A), Teva Ltd. has induced infringement of one or more claims of the '953 Patent;

D. That judgment be entered that Teva Ltd. and Teva USA's direct infringement of the '953 Patent has been willful;

E. That judgment be entered that Teva Ltd.'s inducement of infringement of the '953 Patent has been willful;

F. That an order be entered directing the FDA not to approve Teva Ltd. and Teva USA's ANDA effective any earlier than the expiration date of the '953 Patent;

G. That a permanent injunction be granted preventing Teva Ltd. and Teva USA, their officers, directors, agents, servants, employees, successors and assigns, and all others in concert and privity with it from directly infringing the '953 Patent;

H. That a permanent injunction be granted preventing Teva Ltd., its officers, directors, agents, servants, employees, successors and assigns, and all others in concert and privity with it from inducing infringement of the '953 Patent;

I. That judgment be entered that Teva Ltd. and Teva USA's relevant acts, including Teva Ltd. and Teva USA's willful direct infringement and Teva Ltd.'s willful inducement of infringement, make this case an exceptional case under 35 U.S.C. § 285;

J. That, pursuant to 35 U.S.C. § 285, Plaintiffs recover their reasonable attorney fees incurred in connection with this action;

K. That Plaintiffs recover pre-judgment and post-judgment interest on each and every award;

L. For an assessment of costs against Teva Ltd. and Teva USA; and

M. For such other and further relief as the Court may deem just and proper.

Respectfully Submitted,

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Dated: January 20, 2004

LOCAL CIVIL RULE 11.2 CERTIFICATION

The undersigned hereby certifies that Plaintiffs have filed a patent infringement action in the United States District Court for the District of New Jersey titled *SmithKline Beecham PLC v. Teva Pharmaceuticals USA, Inc.*, 03-CV-4037 (FLW) ("the Teva '803 Patent Case"). While some of the parties in this case are identical to the parties in the Teva '803 Patent Case, and both cases are related to the filing of an ANDA seeking marketing approval for a generic copy of the Avandia® drug product, the cases involve different patents and different issues.

The undersigned further certifies that Plaintiffs have filed two patent infringement actions in the United States District Court for the District of New Jersey titled *SmithKline Beecham PLC v. Dr. Reddy's Laboratories, Ltd.*, 03-CV-4179 (FLW) ("the DRL '803 Patent Case") and *SmithKline Beecham PLC v. Dr. Reddy's Laboratories, Ltd.*, 03-CV-5355 (FLW) ("the DRL '947 Patent Case"). The defendants in the DRL '803 Patent Case and DRL '947 Patent Case are not named in this case or in the Teva '803 Patent Case. Further, while the DRL '803 Patent Case and DRL '947 Patent Case are also related to the filing of an ANDA seeking marketing approval for a generic copy of the Avandia® drug product, as with the Teva '803 Patent Case, the DRL '803 Patent Case and DRL '947 Patent Case involve different patents and different issues then those at issue in this case. The DRL '803 Patent Case and Teva '803 Patent Case have been consolidated for pretrial purposes by the Court, but the DRL '947 Patent Case has not been consolidated with any other case.

Other than the foregoing, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

By: _____
Jason E. Halper (JH-9957)

Dated: January 20, 2004

EXHIBIT A

United States Patent [19]

Hindley

[11] **Patent Number: 5,002,953**

[45] **Date of Patent: Mar. 26, 1991**

[54] **COMPOUNDS**

[75] Inventor: **Richard M. Hindley**, Surrey, England

[73] Assignee: **Beecham Group p.l.c.**, Brentford, England

[21] Appl. No.: **457,272**

[22] Filed: **Dec. 27, 1989**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 238,764, Aug. 30, 1988, abandoned.

[30] **Foreign Application Priority Data**

Sep. 4, 1987 [GB] United Kingdom 8720825
Nov. 30, 1987 [GB] United Kingdom 8727987
Feb. 4, 1988 [GB] United Kingdom 8802454

[51] **Int. Cl.**[5] **C07D 417/12;** A61K 31/125; A61K 31/44; A61K 31/55

[52] **U.S. Cl.** **514/275;** 514/342; 514/367; 514/359; 544/332; 546/280; 548/161; 548/181; 548/183

[58] **Field of Search** 548/182, 181, 161; 546/280; 544/332; 514/369, 367, 342, 275

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

008203 2/1980 European Pat. Off. .

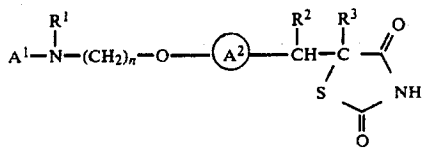
OTHER PUBLICATIONS

Chemical and Pharmaceutical Bulletin, vol. 30, No. 10, Oct. 1982, pp. 3580–3600, Tokyo, JP; T. Sohda et al. "Studies on Antidiabetic Agents, (II.1) Synthesis of 5-[4-(1-methylcyclohexylmethoxy)-benzyl]-thiazolidine-2,4-dione (ADD-3878) and its Derivatives", pp. 3585–3588, 3590, 3591*.

Primary Examiner—Robert Gerstl
Attorney, Agent, or Firm—Hopgood, Calimafde, Kalil, Blaustein & Judlowe

[57] **ABSTRACT**

Compounds of formula (I):



(I)

or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;

R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

R^2 and R^3 each represent hydrogen, or R^2 and R^3 together represent a bond;

A^2 represents a benzene ring having in total up to five substituents; and

n represents an integer in the range of from 2 to 6; pharmaceutical compositions containing such compounds and the use of such compounds and compositions in medicine.

55 Claims, No Drawings

NOVEL COMPOUNDS

This application is a continuation-in-part of U.S. Ser. No. 238,764, filed Aug. 30, 1988, now abandoned.

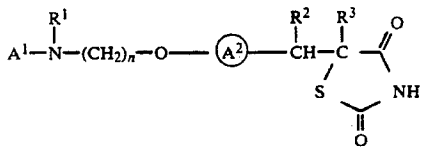
This invention relates to certain substituted thiazolidinedione derivatives, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

European Patent Applications, Publication Numbers 0008203, 0139421, 0155845, 0177353, 0193256, 0207581 and 0208420 relate to thiazolidinedione derivatives which are disclosed as having hypoglycaemic and hypolipidaemic activity. Chem. Pharm. Bull 30 (10) 3580–3600 also relates to certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic activities.

It has now surprisingly been discovered that certain novel substituted-thiazolidinedione derivatives show improved blood-glucose lowering activity and are therefore of potential use in the treatment and/or prophylaxis of hyperglycaemia and are of particular use in the treatment of Type II diabetes.

These compounds are also indicated to be of potential use for the treatment and/or prophylaxis of other diseases including hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders.

Accordingly, the present invention provides a compound of formula (I):



(I)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;

R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

R^2 and R^3 each represent hydrogen, or R^2 and R^3 together represent a bond;

A^2 represents a benzene ring having in total up to five substituents; and

n represents an integer in the range of from 2 to 6.

Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen.

Favoured aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 4 to 7 ring atoms, preferably 5 or 6 ring atoms.

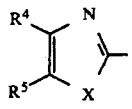
In particular, the aromatic heterocyclyl group comprises 1, 2 or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur or nitrogen.

Suitable values for A^1 when it represents a 5- membered aromatic heterocyclyl group include thiazolyl and oxazolyl, especially oxazolyl.

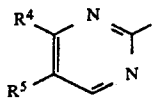
Suitable values for A^1 when it represents a 6- membered aromatic heterocyclyl group include pyridyl or pyrimidinyl.

Suitably R^2 and R^3 each represent hydrogen.

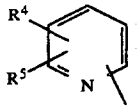
Preferably, A^1 represents a moiety of formula (a), (b) or (c):



(a)



(b)



(c)

wherein:

R^4 and R^5 each independently represents a hydrogen atom, an alkyl group or a substituted or unsubstituted aryl group or when R^4 and R^5 are each attached to adjacent carbon atoms, then R^4 and R^5 together with the carbon atoms to which they are attached form a benzene ring wherein each carbon atom represented by R^4 and R^5 together may be substituted or unsubstituted; and in the moiety of formula (a)

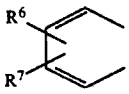
X represents oxygen or sulphur.

Aptly, A^1 represents a moiety of the abovedefined formula (a).

Aptly, A^1 represents a moiety of the abovedefined formula (b).

Aptly. A^1 represents a moiety of the abovedefined formula (c).

In one favoured aspect R^4 and R^5 together represent a moiety of formula (d):



(d)

wherein R^6 and R^7 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

Suitably, R^6 and R^7 each independently represent hydrogen, halogen, alkyl or alkoxy.

Favourably, R^6 represents hydrogen. Favourably, R^7represents hydrogen.

Preferably, R^6 and R^7 both represent hydrogen.

In a further favoured aspect R^4 and R^5 each independently represent hydrogen, alkyl or a substituted or unsubstituted phenyl group and more favourably, R^4 and R^5 each independently represent hydrogen, alkyl or phenyl.

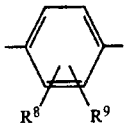
Preferably, for the moiety of formula (a), R^4 and R^5 together represent the moiety of formula (d).

Preferably, for the moieties of formula (b) or (c), R^4 and R^5 both represent hydrogen.

It will be appreciated that the five substituents of A^2 include three optional substituents. Suitable optional

substituents for the moiety A^2 include halogen, substituted or unsubstituted alkyl or alkoxy.

Favourably, A^2 represents a moiety of formula (e):



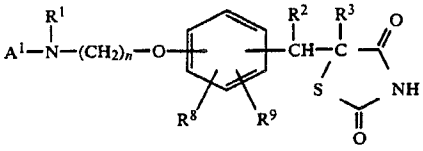
(e)

wherein R^8 and R^9 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

Suitably, R^8 and R^9 each independently represent hydrogen, halogen, alkyl or alkoxy. Preferably, R^8 and R^9 each represent hydrogen.

Favourably, X represents oxygen. Favourably, X represents sulphur.

In one preferred aspect the present invention provides a class of compounds, which fall wholly within the scope of formula (I), of formula (II):



(II)

or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein A^1, R^1, R^2, R^3, and n are as defined in relation to formula (I) and R^8 and R^9 are as defined in relation to formula (e).

Suitably, n represents an integer 2, 3 or 4, notably 2 or 3 and especially 2.

Suitably, R^1 represents hydrogen, alkyl, acyl, especially acetyl, or benzyl.

When R^1 represents an alkyl group, examples of such alkyl groups include methyl and isopropyl. Preferably, R^1 represents a methyl group.

As indicated above a compound of formula (I) may exist in one of several tautomeric forms, all of which are encompassed by the present invention. It will be appreciated that the present invention encompasses all of the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof, including any stereoisomeric forms thereof, whether as individual isomers or as mixtures of isomers.

Suitable substituents for any heterocyclyl group include up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

When used herein the term 'aryl' includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine; preferably chlorine.

When used herein the terms 'alkyl' and 'alkoxy' relate to groups having straight or branched carbon chains, containing up to 12 carbon atoms.

When used herein the term 'acyl' includes alkylcarbonyl groups. Suitable alkyl groups are C_1–C_{12} alkyl groups, especially C_1–C_6 alkyl groups e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl or tert-butyl groups.

Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

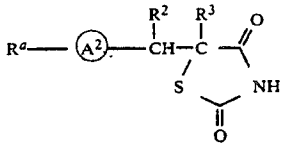
Suitable pharmaceutically acceptable salts include salts of the thiazolidinedione moiety, and, where appropriate, salts of carboxy groups.

Suitable pharmaceutically acceptable salts of the thiazolidinedione moiety include metal salts especially alkali metal salts such as the lithium, sodium and potassium salts.

Suitable pharmaceutically acceptable salts of carboxy groups include metal salts, such as for example aluminium, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine or quinoline.

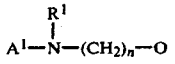
Suitable pharmaceutically acceptable solvates include hydrates.

In a further aspect the present invention also provides a process for the preparation of a compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, which process comprises reacting a compound of formula (III):



(III)

wherein R^2, R^3 and A^2 are as defined in relation to formula (I), and R^a is a moiety convertible to a moiety of formula (f):



(f)

wherein R^1, A^1, and n are as defined in relation to formula (I), with an appropriate reagent capable of converting R^a to the said moiety (f) and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

Suitably, R^a represents R^1HN-$(CH_2)n$—O—wherein R^1 and n are as defined in relation to formula (I).

Suitably, when R^a is R^1HN-$(CH_2)n$—O—, an appropriate reagent capable of converting R^a to a moiety (f) is a compound of formula (IV):

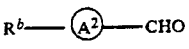
$$A^1-R^x \quad (IV)$$

wherein A^1 is as defined in relation to formula (I) and R^x represents a leaving group.

A suitable leaving group R^x includes a halogen atom, preferably a chlorine or bromine atom, or a thioalkyl group for example a thiomethyl group.

The reaction between the compound of formula (III) and the appropriate reagent may be carried out under conditions suitable to the particular compound of formula (III) and the reagent chosen; thus for example the abovementioned reaction between a compound of formula (III) wherein R^a represents R^1 HN-$(CH_2)n$—O— and the compound of formula (IV), may be carried out in any suitable solvent, for example tetrahydrofuran, at a temperature in the range of between 0° and 60° C.

A compound of formula (III) may be prepared from a compound of formula (V):



(V)

wherein A^2 is as defined in relation to the compound of formula (I) and R^b is a moiety R^a, or a moiety convertible to a moiety R^a; by reaction of the compound of formula (V) with 2,4-thiazolidinedione; and thereafter if required carrying out one or more of the following optional steps:

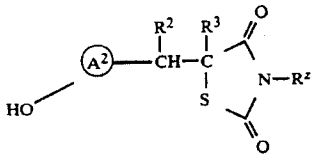
(i) reducing a compound of formula (III) wherein R^2 and R^3 together represent a bond, into a compound of formula (III) wherein R^2 and R^3 each represent hydrogen;

(ii) converting a moiety R^b to a moiety R^a.

The reaction between the compound of formula (V) and 2,4-thiazolidinedione will of course be carried out under conditions suitable to the nature of the compound of formula (V), in general the reaction being carried out in a solvent such as toluene, suitably at an elevated temperature such as the reflux temperature of the solvent and preferably in the presence of a suitable catalyst such as piperidinium acetate or benzoate. Favourably, in the reaction between the compound of formula (V) and 2,4-thiazolidinedione, the water produced in the reaction is removed from the reaction mixture, for example by means of a Dean and Stark apparatus.

When R^a represents R^1HN-$(CH_2)n$—O—, a suitable value for R^b is a hydroxyl group.

The moiety R^b may be converted to the moiety R^a by any suitable means, for example when R^b represents a hydroxyl group and R^a represents $RIHN(CH_2)n$—O— the appropriate conversion may be carried out by coupling a compound of formula (VA):



(VA)

wherein R^2, R^3 and A^2 are as defined in relation to formula (I) and R^z is hydrogen or a nitrogen protecting group, with a compound of formula (VI):

$$R^1NR^x(CH_2)_n—OH \quad (VI)$$

wherein R^1 and n are as defined in relation to formula (I) and R^x is hydrogen or a nitrogen protecting group, in the presence of a suitable coupling agent; and thereafter, if required, carrying out one or more of the following optional steps:

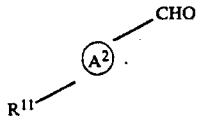
(i) reducing a compound of formula (III) wherein R^2 and R^3 together represent a bond, to a compound of formula (III) wherein R^2 and R^3 each represent hydrogen;

(ii) removing any nitrogen protecting group.

A suitable coupling agent for the coupling reaction between the compound of formula (VA) and (VI) is provided by diethylazodicarboxylate and triphenylphosphine. The coupling reaction may be carried out in any suitable solvent at a low to medium temperature, for example in tetrahydrofuran at a temperature in the range of between 0° and 60° C.

One example of the preparation of a compound of formula (VA) is that wherein a compound falling within formula

(v) of particular formula (VII):



(VII)

wherein A^2 is as defined in relation to formula (I), and R^{11} represents a hydroxyl group or a protected hydroxyl group, is reacted with 2,4-thiazolidinedione; and thereafter if required removing any protecting group.

Preferably, R^{11} represents a benzyloxy group.

Suitable conditions for the reaction between a compound of formula (VII) and 2,4-thiazolidinedione are those defined above in relation to the reaction between the compounds of formula (V) and 2,4-thiazolidinedione.

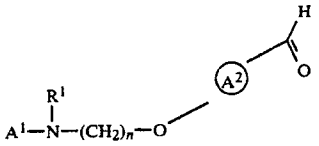
The compounds of formula (IV), (VI) and (VII) are either known compounds or are prepared using methods analogous to those used to prepare known compounds.

Suitable protecting groups in any of the abovementioned reactions are those used conventionally in the art. Thus, for example, a suitable nitrogen protecting group is a benzyl group or a benzyloxycarbonyl group and a suitable hydroxyl protecting group is a benzyl group.

The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example when R^{11} represents a benzyloxy group such group may be prepared by treatment of the appropriate compound of formula (VII), wherein R^{11} is a hydroxyl group with a benzyl halide, such as benzyl bromide, and thereafter when required the benzyl group may be conveniently removed using a mild ether cleavage reagent such as trimethylsilyliodide.

A compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate

thereof, may also be prepared by reacting a compound of formula (VIII):



(VIII)

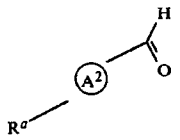
wherein R^1, A^1, A^2, and n are as defined in relation to formula (I) with 2,4-thiazolidinedione; and thereafter if required carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

The reaction between a compound of formula (VIII) and 2,4-thiazolidinedione may suitably be carried out under analogous conditions to those used in the reaction between a compound of formula (V) and 2,4-thiazolidinedione.

A compound of formula (VIII) may be prepared by reacting a compound of formula (IX):



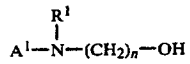
(IX)

wherein A^2 is as defined in relation to formula (I) and R^a is as defined in relation to formula (III), with an appropriate reagent capable of converting R^a to the above defined moiety (f).

Suitable values for R^a include those described above in relation to the compound of formula (III). Thus R^a may represent R^1HN-(CH_2)n—O—, as defined above, and hence the appropriate compound of formula (IX) may be reacted with a reagent of the abovedefined formula (IV) to provide the required compound of formula (VIII).

Suitable reaction conditions for the reaction of the compound of formula (IX) and the appropriate reagent may include those described above in relation to the preparation of compound (III) with the said appropriate reagent.

Preferably, for the compound of formula (IX), R^a represents a leaving group, especially a fluorine atom. When R^a represents a leaving group, preferably a fluorine atom, a particularly appropriate reagent is a compound of formula (X):



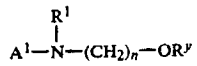
(X)

wherein R^1, A^1, and n are as defined in relation to formula (I).

The reaction between the compounds of formulae (IX) and (X) may be carried out under any suitable conditions, for example in a solvent such as dimethylformamide or dimethylsulphoxide at an elevated temperature for example in the range of between 100° to 150° C., suitably in the presence of a base such as sodium hydride or potassium carbonate.

In the compound of formula (IX) R^a may also represent a hydroxyl group.

When R^a, in the compound of formula (IX), represents a hydroxyl group a particularly appropriate reagent is a compound of the above defined formula (X) or a compound of formula (XA):



(XA)

wherein A^1, R^1 and n are as defined in relation to formula (X) and R^y represents a tosylate or mesylate group.

The reaction between the compound of formula (IX) wherein R^a is a hydroxyl group and the reagent of the abovedefined formula (X) may suitably be carried out in an aprotic solvent, such as tetrahydrofuran, at low to medium temperature, for example at ambient temperature, and preferably in the presence of a coupling agent such as that provided by triphenylphosphine and diethylazodicarboxylate.

The reaction between the compound of formula (IX), wherein R^a is a hydroxyl group, and the reagent of the abovedefined formula (XA) may be carried out in an aprotic solvent, such as dimethylformamide, at a low to elevated temperature, for example in the range of from 50° C. to 120° C. and preferably in the presence of a base, such as sodium hydride.

The compound of formula (XA) may be prepared from the corresponding compound of formula (X) by reaction with either a tosyl halide or a mesyl halide in a solvent such as pyridine.

The compounds of formula (IX) are known compounds or compounds prepared by methods analogous to those used to prepare known compounds, for example 4-fluorobenzaldehyde and 4-hydroxybenzaldehyde are known commercially available compounds.

The reagent of formula (X) may be prepared by reacting a compound of the hereinabove defined formula (IV), with a compound of the hereinbefore defined formula (VI) and thereafter if required removing any nitrogen protecting group using the appropriate conventional conditions.

The reaction between the compounds of formula (IV) and (VI) may be carried out under any suitable conditions, such as in solvent, for example in an aprotic solvent such as tetrahydrofuran, at a low to medium temperature, for example a temperature in the range of from 0° to 60° C.

Favourably when R^1 represents hydrogen the reaction is carried out using the compound of formula (VI) as a solvent at a low to elevated temperature, suitably an elevated temperature such as in the range of between 100° and 170° C.

The abovementioned conversion of a compound of formula (I) into a further compound of formula (I) includes the following conversions:

(a) reducing a compound of formula (I) wherein R^2 and R^3 together represent a bond, to a compound of formula (I) wherein R^2 and R^3 each represent hydrogen; and

(b) converting one group R^1 into another group R^1.

The conversion of a compound of formula (I) to a further compound of formula (I) may be carried out by using any appropriate conventional procedure.

A suitable reduction method for the abovementioned conversion (a) includes catalytic reduction or the use of a metal/solvent reducing system.

Suitable catalysts for use in the catalytic reduction are palladium on carbon catalysts, preferably a 10% palladium on charcoal catalyst; the reduction being carried out in a solvent, for example dioxan, suitably at ambient temperature.

Suitable metal/solvent reducing systems include magnesium in methanol.

The abovementioned reduction of a compound of formula (III) wherein R^2 and R^3 together represent a bond to a compound of formula (III) wherein R^2 and R^3 each represent hydrogen, may be carried out under analogous conditions to those referred to above in conversion (a) of the compound of formula (I).

In the abovementioned conversion (b), suitable conversions of one group R^1 into another group R^1 includes converting a group R^1 which represents hydrogen into a group R^1 which represents an acyl group.

The conversion of a compound of formula (I) wherein R^1 represents hydrogen into a compound of formula (I) wherein R^1 represents acyl may be carried out using any appropriate conventional acylation procedure, such as by treating an appropriately protected compound of formula (I) with an acylating agent. For example acetic anhydride may be used to prepare the compound of formula (I) wherein R^1 is acetyl.

It will be appreciated that in the abovementioned conversions (a) and (b), any reactive group in the compound of formula (I) would be protected, according to conventional chemical practice, where necessary.

Where appropriate the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof may be prepared as individual isomers using conventional chemical procedures.

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties:

The present invention accordingly provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

Thus the present invention provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia.

In a further aspect the present invention also provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of hyperlipidaemia.

As indicated hereinbefore the present invention also provides a compound of formula (I) or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof for use in the treatment of hypertension, cardiovascular disease and certain eating disorders.

A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of the general formula (I), or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate, sodium lauryl sulphate or sucrose.

Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in the range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a hyperglycaemic human or non-human mammal in need thereof.

The present invention further provides a method for the treatment of hyperlipidaemia in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, to a hyperlipidaemic human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of hyperglycaemic humans, and/or the treatment and/or prophylaxis of hyperlipidaemic human, the compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be taken in doses, such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of from 0.1 to 6000 mg, and more usually about 1 to 1500 mg.

In the treatment and/or prophylaxis of hyperglycaemic non-human mammals, especially dogs, the active ingredient may be adminstered by mouth, usually once

or twice a day and in an amount in the range of from about 0.025 mg/kg to 25 mg/kg, for example 0.1 mg/kg to 20 mg/kg. Similar dosage regimens are suitable for the treatment and/or prophylaxis of hyperlipidaemia in non-human mammals.

The dosages regimens for the treatment of hypertension, cardiovascular disease and eating disorders will generally be those mentioned above in relation to hyperglycaemia.

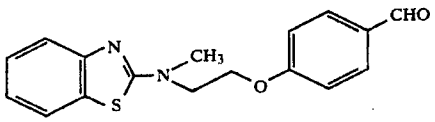
In a further aspect the present invention provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia.

The present invention also provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidaemia, hypertension, cardiovascular disease or certain eating disorders.

The following Procedures and Examples illustrate the invention but do not limit it in any way.

PREPARATION 1

4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]-benzaldehyde

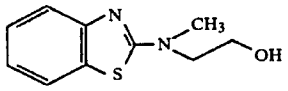


A mixture of 4-fluorobenzaldehyde (1.5g) and 2[N-methyl-N-(2-benzothiazolyl)amino]ethanol (2.4g) in sulphoxide (50 ml) containing anhydrous potassium carbonate (2 g) was stirred at 100° C. for 24 hours. The mixture was cooled to room temperature and added to water (300 ml). The aqueous solution was extracted with diethyl ether (2×300 ml). The organic extracts were washed with brine (1×300 ml), dried ($MgSO_4$), filtered and evaporated to dryness. The title compound was obtained as a waxy solid following chromatography on silica-gel in 1% methanol in dichloromethane.

^1H NMR δ ($CDCl_3$) 3.2 (3H, s); 3.8 (2H, t); 4.2 (2H, t); 6.8–7.8 (8H, complex); 9.8 (1H, s).

PREPARATION 2

2-[N-Methyl-N-(2-benzothiazolyl)amino]ethanol

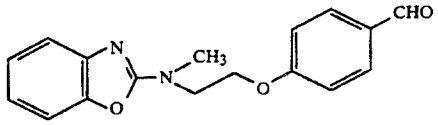


A mixture of 2-chlorobenzothiazole (8.5 g) and 2-methylaminoethanol (20 ml) was heated at 120° C. under pressure in a sealed, glass lined, stainless steel reaction vessel for 18 hours. After cooling, the oil was added to water (100 ml), extracted with dichloromethane (2×100 ml), the organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness Chromatography of the residual oil on silica-gel in 2½% methanol in dichloromethane gave the title compound which was used in Preparation 1 without further purification.

^1H NMR δ ($CDCl_3$) 3.15 (3H, s); 3.4–4.0 (4H, m); 4.7 (1H, broad s, exchanges with D_2O; 6.8–7.6 (4H, complex).

PREPARATION 3

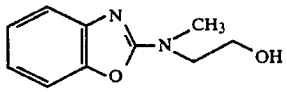
4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde



To a solutiOn of 2-[N-methyl-N-(2-benzoxazolyl) amino]ethanol (9.6 g), triphenylphosphine (13.1 g) and 4-hydroxybenzaldehyde (6.1 g) in dry tetrahydrofuran (150 ml) was added dropwise a solution of diethyl azodicarboxylate (9.0 g) in dry tetrahydrofuran (30 ml), under a blanket of nitrogen with stirring at room temperature. The solution was stirred overnight at room temperature following which the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (300 ml), filtered and the ether solution was washed with dilute sodium hydroxide solution (200 ml), saturated brine (200 ml), dried ($MgSO_4$), filtered and the solvent evaporated. The title compound (mp 97°–98° C.) was obtained after chromatography on silica-gel, eluting with dichloromethane. ^1H NMR δ ($CDCl_3$) 3 30 (3H, s); 3.85 (2H, t); 4.30 (2H, t) 6.80–7.85 (8H, complex); 9.85 (1H, s).

PREPARATION 4

2-[N-Methyl-N-(2-benzoxazolyl)amino]ethanol

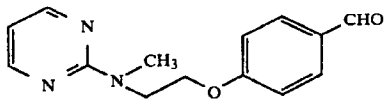


A solution of 2-chlorobenzoxazole (15.4 g) in dry tetrahydrofuran (50 ml) was added dropwise to an ice cooled solution of 2-methylaminoethanol (15.0 g) in dry tetrahydrofuran (100 ml) with stirring and protection from atmospheric moisture. The mixture was stirred at 0° C. for 1 hour, allowed to warm to room temperature and stirred for a further 2 hours. The solvent was removed under reduced pressure, the product was dissolved in ethyl acetate (200 ml) and washed with brine (2×150 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. Chromatography of the residue on silica-gel in dichloromethane gave the title compound (mp 62°–3° C.) which was used in Preparation 3 without further purification.

^1H NMR δ ($CDCl_3$) 3.12 (3H s); 3.4–4.0 (4H, m); 4.7 (1H, s, exchanges with D_2O); 6.8–7.4 (4H, complex).

PREPARATION 5

4-[2-(N-Methyl-N-(2-pyrimidinyl)amino)ethoxy]benzaldehvde

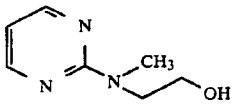


A mixture of 4-fluorobenzaldehyde (12 ml) and 2-[N-methyl-N-(2-pyrimidinyl)amino]ethanol (10.05 g) in dry dimethyl sulphoxide (50 ml) containing anhydrous potassium carbonate (15 g) was stirred at 120° C. for 6 hours. The mixture was cooled to room temperature and added to water (200 ml). The aqueous solution was extracted with ethyl acetate (2×300 ml), the organic extracts washed with brine, dried ($MgSO_4$) and evaporated. The title compound was obtained as an oil following chromatography on silica-gel in 2% methanol in dichloromethane.

^1H NMR δ ($CDCl_3$) 3.3 (3H, s); 3.8–4.4 (4H, complex); 6.5 (1H, t); 7.0 (2H, d); 7.8 (2H, d); 8.3 (2H, d); 9.9 (1H, s).

PREPARATION 6

2-[N-Methyl-N-(2-pvrimidinyl)amino]ethanol

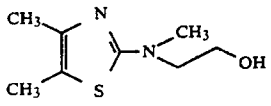


A mixture of 2-chloropyrimidine (10 g) and 2-methylaminoethanol in dry tetrahydrofuran (100 ml) was boiled under reflux for 3 hours. The solution was cooled, water (200 ml) was added, the mixture extracted with dichloromethane, the organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness. The residual oil was used in Preparation 5 without further purification.

^1H NMR δ ($CDCl_3$) 3.2 (3H, s); 3.5–3.9 (4H, m); 4.6 (1H, s, exchanges with D_2O); 6.4 (1H, t); 8.2 (2H, d).

PREPARATION 7

2-N-Methyl-N-(2-[4,5-dimethylthiazolyl])amino]ethanol

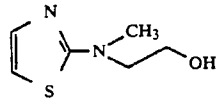


A solution of 2-chloro-4,5-dimethylthiazole (13.2 g) and 2-methylaminoethanol (40 ml) in pyridine (100 ml) was boiled under reflux for 20 hours. After cooling, the oil was added to water (300 ml) and extracted with ethyl acetate (3×200 ml). The organic extracts were washed with brine (2×200 ml), dried ($MgSO_4$), filtered and evaporated to dryness to leave the title compound which was used in Preparation 14 without further purification.

^1H NMR δ ($CDCl_3$) 2.15 (3H, s); 2.20 (3H, s); 3.1 (3H, s); 3.4–3.9 (4H, m); 5.25 (1H, broad s, exchanges with D_2O).

PREPARATION 8

2-[N-Methyl-N-(2-thiazolyl)amino]ethanol

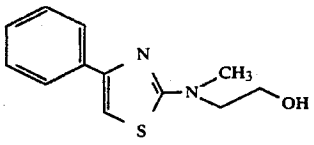


The title compound was prepared as an oil from 2-bromothiazole (15 g) and 2-0methylaminoethanol (45 ml) by an analogous procedure to that described in Preparation 7

^1H NMR δ ($CDCl_3$) 3.1 (3H, 2); 3.4–3.0 (4H, m); 4.8 (1H, broad s, exchanges with D_2O); 6.4 (1H, d); 7.0 (1H, d).

PREPARATION 9

2-[N-Methyl-N-(2-(4-phenylthiazolyl))amino]ethanol

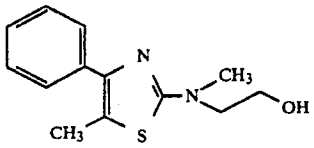


The title compound was prepared as an oil from 2-chloro-4-phenylthiazole (13.5 g) and 2-methylaminoethanol (40 ml) by an analogous procedure to that described in Preparation 7.

1H NMR δ ($CDCl_3$) 3.15 (3H, s); 3.6–4.0 (4H, m); 4.6 (1H, broad s, exchanges with D_2O); 6.7 (1H, s); 7.2–7.9 (5H, complex).

PREPARATION 10

2-[N-Methyl-N-(2-(4-phenyl-5-methylthiazolyl)-)amino]ethanol

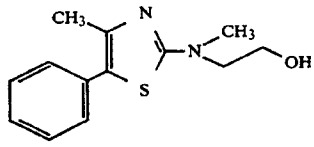


The title compound was prepared as an oil from 2-chloro-4-phenyl-5-methylthiazole (18.9 g) and 2-methylaminoethanol (50 ml) by an analogous procedure to that described in Preparation 7.

^1H NMR δ ($CDCl_3$) 2.38 (3H, s); 3.0 (3H, s); 3.45–3.85 (4H, m); 5.1 (1H, broad s, exchanges with D_2O); 7.1–7.7 (5H, complex).

PREPARATION 11

2-[N-Methyl-N-(2-(4-methyl-5-phenylthiazolyl)-)amino]ethanol

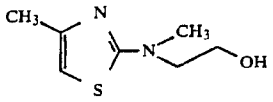


The title compound was prepared as an oil from 2-chloro-4-methyl-5-phenylthiazole (14.8 g) and 2-methylaminoethanol (40 ml) by an analogous procedure to that described in Preparation 7.

^1H NMR δ ($CDCl_3$) 2.35 (3H, s); 3.1 (3H, s); 3.5–4.0 (4H, m); 5.1 (1H, broad s, exchanges with D_2O); 7.1–7.5 (5H, complex).

PREPARATION 12

2-[N-Methyl-N-(2-(4-methylthiazolyl))amino]ethanol

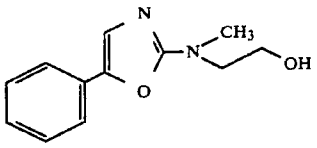


The tital compound was prepared, by an analogous procedure to that described in Preparation 7, and was used in the next stage without further purification.

^{1}H NMR δ ($CDCl_3$) 2.25 (3H, s); 3.1 (3H, s); 3.55–3.95 (4H, m); 4.9 (1H, broad s, exchanges with D_2O); 6.1 (1H, s).

PREPARATION 13

2-[N-Methyl-N-[2- (5-phenyloxazolyl)]amino]ethanol

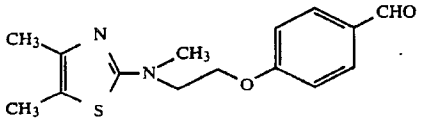


A solution of 2-chloro-5-phenyloxazole (8.3 g) and 2-methylaminoethanol (30 ml) was stirred at 50° C. for 10 minutes. After cooling the oil was added to water (250 ml) and extracted with ethyl acetate (2×150 ml). The organic extracts were washed with brine (2×100 ml), dried ($MgSO_4$), filtered and evaporated to dryness to leave the title compound (m.p. 73°–75° C.).

^{1}H NMR δ ($CDCl_3$) 3.2 (3H, s); 3.6 (2H, t); 3.85 (2H, t); 3.9 (1H, broad s, exchanges with D2O); 7.0 (1H, s); 7 2–7.55 (5H, complex).

PREPARATION 14

4-[2-(N-Methyl-N-(2-(4,5-dimethylthiazolyl)amino) ethoxy)]benzaldehyde

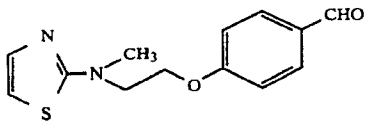


The title compound was prepared from 2-[N-methyl-N(2-(4,5-dimethylthiazolyl))amino]ethanol (13.2 g) and 4-fluorobenzaldehyde (23.1 g) by an analogous procedure to that described in Preparation 5.

^{1}H NMR δ ($CDCl_3$) 2.15 (3H, s); 2.2 (3H, s); 3.18 (3H, s); 3.8 (2H, t); 4.3 (2H, t); 7.0 (2H, d); 7.8 (2H, d); 10.0 (1H, s).

PREPARATION 15

4-[2-(N-Methyl-N-(2-thiazolyl)amino)ethoxy]benzaldehyde

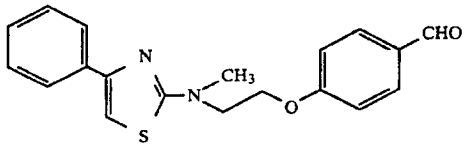


The title compound was prepared from 2-[N-methyl-N-(2-thiazolyl)amino]ethanol (10.7 g) and 4-fluorobenzaldehyde (15.9 g) by an analogous procedure to that described in Preparation 5.

^{1}H NMR δ ($CDCl_3$) 3.15 (3H, s); 3.9 (2H, t); 4.4 (2H, t); 6.5 (1H, d); 7.0 (2H, d); 7.15 (1H, d); 7.8 (2H, d); 9.9 (1H, s).

PREPARATION 16

4-[2-(N-Methyl-N-(2-(4-phenylthiazolyl)amino)ethoxy)]benzaldehyde

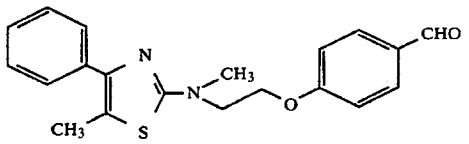


The title compound was prepared from 2-[N-methyl-N-(2-(4-phenylthiazolyl))amino]ethanol (16.1 g) and 4-fluorobenzaldehyde (17.4 g) by an analogous procedure to that described in Preparation 5.

^{1}H NMR δ ($CDCl_3$) 3.2 (3H, s); 3.95 (2H, t); 4.3 (2H, t); 6.7 (1H, s); 6.95–7.9 (9H, complex); 9.9 (1H, s).

PREPARATION 17

2-(N-Methyl-N-(2-(4-phenyl-5-methylthiazolyl)amino) ethoxy)1benzaldehyde

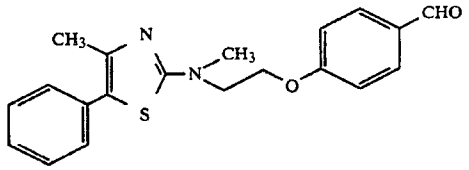


The title compound was prepared from 2-[N-methyl-N-(2-(4-phenyl-5-methylthiazolyl))amino]ethanol (13 g) and 4-fluorobenzaldehyde (9.8 g) by a similar procedure to that described in Preparation 5.

^{1}H NMR δ ($CDCl_3$) 2.35 (3H, s); 3.1 (3H, s); 3.8 (2H, t); 4.2 (2H, t); 6.85–7.8 (9H, complex); 9.85 (1H, s).

PREPARATION 18

4-[2-(N-Methyl-N-(2-(4-methyl-5-phenyl-thiazolyl-)amino) ethoxy)]benzaldehyde

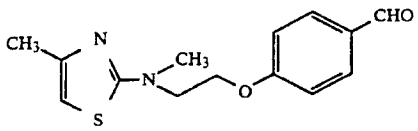


The title compound was prepared from 2-[N-methyl-N-(2-(4methyl-5-phenylthiazolyl))amino]ethanol (13 g) and 4-fluorobenzaldehyde (13 g) by an analogous procedure to that described in Preparation 5.

^{1}H NMR δ ($CDCl_3$) 2.36 (3H, s); 3.2 (3H, s); 3.9 (2H, t); 4.35 (2H, t); 7.05 (2H, d); 7.2–7.5 (5H, complex); 7.85 (2H, d); 9.95 (1H, s).

PREPARATION 19

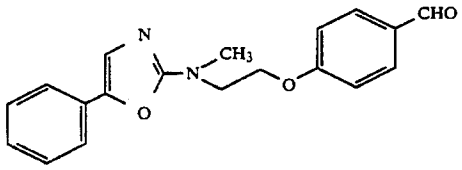
4-[2-(N-Methyl-N-(2-(4-methylthiazolyl))amino)ethoxy]benzaldehyde



The title compound was prepared from 2-[N-methyl-N-(2-(4-methylthiazolyl))amino]ethanol (12 g) and 4-fluorobenzaldehyde (14.3 g) by an analogous procedure to that described in Preparation 5. ^{1}H NMR 4 ($CDCl_3$) 2.25 (3H, s); 3.2 (3H, s); 3.9(2H, t); 4.3 (2H, t); 6.1 (1H, s); 7.05 (2H, d); 7.85 (2H, d); 9.95 (1H, s).

PREPARATION 20

4-[2-(N-Methyl-N-[2-(5-phenyloxazolyl)]amino)ethoxy]benzaldehyde

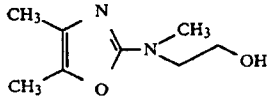


The title compound was prepared from 2-[N-methyl-N-(2-(5-phenyloxazolyl))amino]ethanol (9.3 g) and 4-fluorobenzaldehyde (7.9 g) by an analogous procedure to that described in Preparation 5.

^{1}H NMR δ ($CDCl_3$) 3.25 (3H, s); 3.85 (2H, t); 4.3 (2H, t); 6.95–7.6 (8H, complex); 7.8 (2H, d); 9.9 (1H, s).

PREPARATION 21

2-[N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino]-ethanol.

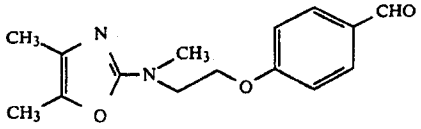


A solution of 2-chloro-4,5-dimethyloxazole (5 g) and 2-methylaminoethanol (15 ml) was stirred at 120° C. for 40 minutes. After cooling the oil was added to water (200 ml) and extracted with dichloromethane (3×200 ml). The organic extracts were washed with brine (2×100 ml), dried ($MgSO_4$), filtered and evaporated to dryness to leave the title compound as a waxy solid, which was used in Preparation 22 without further purification.

^{1}H NMR δ ($CDCl_3$) 1.95 (3H, s); 2.10 (3H, s); 3.05 (3H, s); 3.5 (2H, t); 3.8 (2H, t); 4.4 (1H, broad s, exchanges with D_2O).

PREPARATION 22

4-[2-(N-Methyl-N-2-(4,5-dimethyloxazolyl)]amino) ethoxy]benzaldehyde

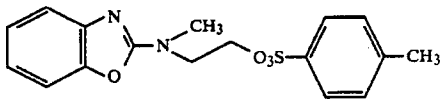


To a stirred solution of 2-[N-methyl-N-[2-(4,5dimethyloxazolyl)amino]ethanol (2.7 g) in DMF (60 ml), under an atmosphere of nitrogen, was added portionwise sodium hydride (0.7 g; 60% dispersion in oil). After the vigorous reaction had subsided, 4-fluorobenzaldehyde (2.9 g) was added and the reaction mixture was heated to 80° C. for 16 hours. After cooling, the mixture was added to water (400 ml). The aqueous solution was extracted with diethyl ether (3×250 ml). The organic extracts were washed with brine (2×100 ml), dried ($MgSO_4$), filtered and evaporated to dryness. The title compound was obtained as an oil following chromatography of the residue on silica-gel in 1% methanol in dichloromethane.

^{1}H NMR δ ($CDCl_3$) 1.95 (3H, s); 2.15 (3H, s); 3.15 (3H, s); 3.8 (2H, t); 4.25 (2H, t); 7.0 (2H, d); 7.9 (2H, d); 10.0 (1H, s).

PREPARATION 23

2-(N-(2-Benzoxazolyl)-N-methylamino)ethanol 4-toluenesulphonyl ester

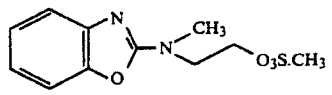


4-Toluenesulphonyl chloride (19.0 g) was added portionwise to a solution of N-(2-benzoxazolyl)-N-methylaminoethanol (19.2 g) in dry pyridine (100 ml) at room temperature. The mixture was stirred at room temperature for 3 hours, added to water (500 ml) and extracted with dichloromethane (3×250 ml). The combined extracts were washed with 2M hydrochloric acid (3×250 ml), saturated sodium bicarbonate solution (250 ml) and brine (250 ml), dried ($MgSO_4$), filtered and evaporated. The title compound was obtained pure following crystallisation from ethanol (m.p. 119°–121° C.).

^{1}H NMR δ (DMSO-d_6) 2.25 (3H, s); 3.05 (3H, s); 3.75 (2H, t); 4.35 (2H, t); 7.0–7.4 (6H, complex); 7.70 (2H, d).

PREPARATION 24

2-(N-(2-Benzoxazolyl)-N-methylamino)ethanol methanesulphonyl ester

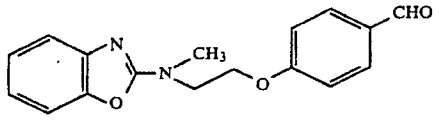


The title compound (m.p. 97°–8° C.) was prepared from N-(2-benzoxazolyl)-N-methylaminoethanol (19.2 g) and methanesulphonyl chloride (11.5 g) by a similar procedure to that used in Preparation 23.

^{1}H NMR δ ($CDCl_3$) 2.90 (3H, s); 3.25 (3H, s); 3.7 (2H, t); 4.5 (2H, t); 6.90–7.4 (4H, complex).

PREPARATION 25

4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde

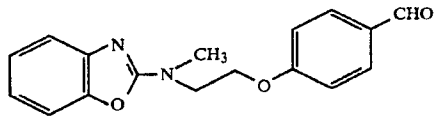


To a solution of 4-hydroxybenzaldehyde (7.32 g) in dry dimethylformamide (100 ml) was added portionwise sodium hydride (60%, 2.4 g) with stirring at room temperature under nitrogen. When gas evolution ceased a solution of 2-(N-methyl-N-(2-benzoxazolyl)amino)ethanol 4-toluenesulphonyl ester (17.3 g) in dry dimethylformamide was added dropwise The mixture was heated to 80° C. and stirred at this temperature overnight. After cooling, the solution was poured into iced water (1 litre), extracted with ethyl acetate (3×500 ml), and the combined extracts were washed with sodium hydroxide solution (2M; 500 ml) and brine (500 ml), dried ($MgSO_4$), filtered and evaporated. The title compound (m.p. 96°–98° C.) was obtained pure after crystallisation from ethanol.

^{1}H NMR δ (DMSO-d_6) 3.25 (3H, s); 3.95 (2H, t); 4.40 (2H, t); 6.90–7.40 (6H, complex); 7.85 (2H, d); 9.90 (1H, s).

PREPARATION 26

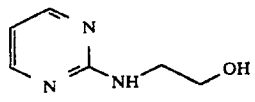
4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde



The title compound was prepared from 4-hydroxy benzaldehyde (1.22 g) and 2-(N-methyl-N-(2-benzoxazolyl)-amino)ethanol methanesulphonyl ester (2.7 g) in a similar manner to that described in Preparation 25.

PREPARATION 27

2-(2-Pyrimidinylamino)ethanol

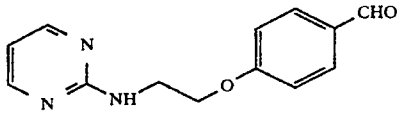


2-Chloropyrimidine (5 g) and ethanolamine (15 ml) were stirred for 2 hours at 140° C. After cooling, the mixture was added to water (200 ml) and continuously extracted with ethyl acetate (500 ml) for 16 hours. The organic extract was dried ($MgSO_4$), filtered and evaporated to dryness. The title compound was obtained as a solid (m.p. 66° C.), following chromatography on silica-gel in 3% methanol in dichloromethane.

^{1}H NMR δ ($CDCl_3$) 3.55 (2H, complex); 3.8 (2H, t); 4.3 (1H, broad s, exchanges with D_2O); 6.1 (1H, broad s, exchanges with D_2O); 6.55 (1H, t); 8.3 (2H, d).

PREPARATION 28

4-[2-(2-Pyrimidinylamino)ethoxy]benzaldehyde

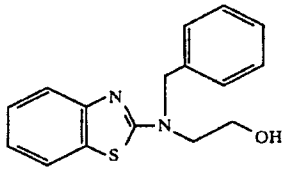


Sodium hydride (1.2 g; 60% dispersion in oil) was added portionwise to a stirred solution of 2-(2-pyrimidinyl amino)ethanol (4 g) in DMF (140 ml) under an atmosphere of nitrogen. After the vigorous reaction had subsided 4-fluorobenzaldehyde (5.35 g) was added and the solution heated to 80° C. for 20 hours. After cooling the mixture was added to water (500 ml) and extracted with diethyl ether (3×300 ml). The organic extracts were washed with brine (2×200 ml), dried ($MgSO_4$), filtered and evaporated to dryness. Chromatography of the residue on silica gel in 2% methanol in dichloromethane afforded the title compound, which was used in the next stage without further purification.

^{1}H NMR δ ($CDCl_3$) 3.8 (2H, complex); 4.2 (2H, t); 5.7 (1H, broad s, exchanges with D_2O); 6.5 (1H, t); 7.0 (2H, d); 7.8 (2H, d); 8.3 (2H, d); 9.9 (1H, s).

PREPARATION 29

2-(N-(2-Benzothiazolyl)-N-benzylamino)ethanol

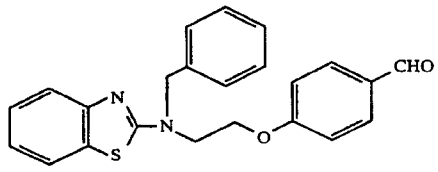


2-Chlorobenzothiazole (13 g) and 2-(benzylamino)ethanol (29 g) were heated together in a sealed vessel at 120° C. for 20 h. After cooling, the reaction mixture was dissolved in ethyl acetate (200 ml) and the solution was washed with saturated aqueous sodium hydrogen carbonate (3×100 ml), water (3×100 ml) and brine (100 ml), dried over anhydrous magnesium sulphate and evaporated to give the title compound (m.p. 95°–96° C.; dichloromethane/hexane).

^{1}H NMR δ ($CDCl_3$) 3.8 (4H, m); 4.5 (1H, broad s, exchanges with D_2O); 4.7 (2H, s); 6.9–7.7 (9H, complex).

PREPARATION 30

4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy)benzaldehyde



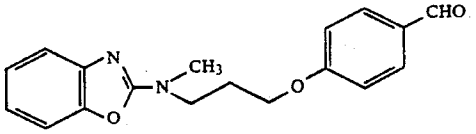
The title compound was prepared from 2-(N-(2-benzothiazolyl)-N-benzylamino)ethanol (8.25 g) and 4-

fluorobenzaldehyde (3.6 g) by an analogous procedure to that described in Preparation 22.

^{1}H NMR δ ($CDCl_3$) 4.0 (2h, t); 4.4 (2H, t); 4.9 (2H, s); 6.9–8.0 (13H, complex); 10.0 (1H, s).

PREPARATION 31

4-3-(N-Methyl-N-(2-benzoxazolyl)-amino)propoxy]-benzaldehyde

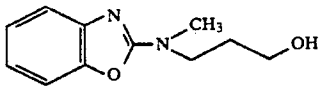


The title compound was prepared from 3-[(N-(2-benzoxazolyl)-N-methyl)amino]propan-1-ol (7.5 g) and 4-fluorobenzaldehyde (6.78 g) by a similar procedure to that described in Preparation 22.

^{1}H NMR δ ($CDCl_3$) 2.0–2.4 (2H, complex); 3.2 (3H, s); 3.75 (2H, t); 4.2 (2H, t); 6.8–7.5 (6H, complex); 7.8 (2H, d); 9.9 (1H, s).

PREPARATION 32

3-[(N-(2-Benzoxazolyl)-N-methyl)amino]propan-1-ol

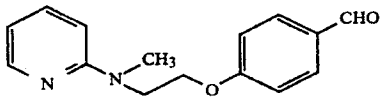


2-Chlorobenzoxazole (15.36 g) in dry tetrahydrofuran (50 ml) was added dropwise to a mixture of 3-N-methylaminopropan-1-ol (9.8 g) and triethylamine (20.2 g) in dry tetrahydrofuran (130 ml) with stirring, at room temperature. After stirring at room temperature overnight the solvent was evaporated. The residue was dissolved in dichloromethane (150 ml), washed with water (3×100 ml), brine (150 ml), dried ($MgSO_4$), filtered and evaporated. The title compound was obtained as an oil following chromatography on silica-gel in 2.5–3% methanol in dichloromethane.

^{1}H NMR δ ($CDCl_3$) 1.8–2 1 (2H, complex); 3.2 (3H, s); 3.5–3.85 (4H, complex); 4.3 (1H, broad s, exchanges with D_2O); 6.8–7.5 (4H, complex).

PREPARATION 33

4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzaldehyde

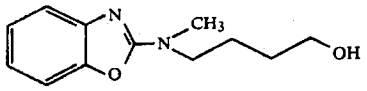


The title compound was prepared from 2-(N-methyl-N-(2-pyridyl)amino)ethanol (8.9 g) and 4-fluorobenzaldehyde by a similar procedure to that described in Preparation 22.

^{1}H NMR δ ($CDCl_3$) 3.2 (3H, s); 3.8 (2H, t); 4.2 (2H, t); 6.4 (2H, t); 6.9 (2H, d); 7.3 (1H, complex); 7.75 (2H,d); 8.15 (1H,d); 9.9 (1H, s).

PREPARATION 34

4-[N-(2-Benzoxazoyl)-N-methylamino1butan-1-ol

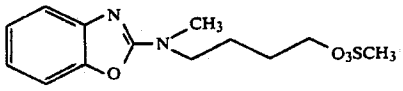


2-Chlorobenzoxazole (15.35 g) was added dropwise over 10 minutes to a stirred solution of 4-(N-m®thylamino)butan-1-ol (10.3 g) and triethylamine (20.3 g) in dry tetrahydrofuran (150 ml). The mixture was stirred at room temperature overnight, and then heated at reflux for a further 2 h. The resulting mixture was cooled and the solvent was evaporated. The residue was dissolved in dichloromethane (500 ml), washed with saturated sodium bicarbonate solution (3×300 ml) and brine (500 ml), dried and evaporated to afford the title compound as an oil.

^{1}H NMR δ ($CDCl_3$) 1.5–2.0 (4H, complex); 3.1 (3H,s); 3.4–3.9 (5H, complex; reduced to 4H after D20 exchange); 6.9–7.4 (4H, complex)

PREPARATION 35

4-[(N-(2-BenzoxazolVl)-N-methyl)amino1butan-l-ol methanesulohonyl ester

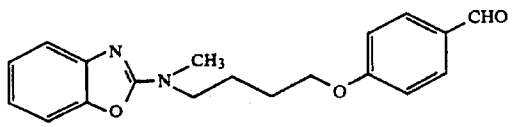


Methanesulphonyl chloride (3.15 g) was added dropwise to a stirred, ice-cooled solution of 4-[N-(2-benzoxazolyl)-N-methylamino]butan-1-ol (5.5 g) and 4-dimethylaminopyridine (0.15 g) in pyridine (100 ml). The mixture was allowed to warm to room temperature overnight, and then diluted with water (500 ml), and extracted with dichloromethane (3×200 ml). The combined extracts were washed with saturated sodium bicarbonate solution (3×200 ml), and brine (200 ml), then dried and the solvent evaporated to afford an oil. More of this oil was obtained from the acidic aqueous layers by means of adjusting the pH to 4.5 with solid potassium carbonate, re-extracting with dichloromethane (3×200 ml), and drying and evaporating these dichloromethane layers. The combined impure product fractions were chromatographed on silica gel with 2% methanol in dichloromethane as eluent to afford the title compound as an oil.

^{1}H NMR δ ($CDCl_3$) 1.80(4H,complex); 3.05(3H,s); 3.25(3H,s); 3.60(2H,complex); 4.30(2H,complex); 6.90–7.40(4H, complex)

PREPARATION 36

4-[4-(N-Methyl-N-(2-benzoxazolyl)amino)butoxy]benzaldehyde

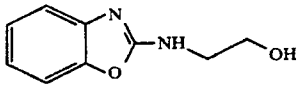


The title compound was prepared from 4-hydroxybenzaldehyde (1.71 g) and 4-[N-(2-benzoxazolyl)-N-methylamino]butan-1-ol methanesulphonyl ester (3.80 g) by a similar procedure to that used in Preparation 26.

^{1}H NMR δ ($CDCl_3$) 1.70–1.95(4H, complex); 3.20(3H,s); 3.55(2H, complex); 4.00(2H, complex); 6.80–7.40(6H, complex) 7.75(2H,d); 9.90(1H,s)

PREPARATION 37

2-[N-(2-Benzoxazolyl)amino]ethanol

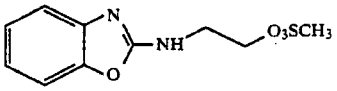


A solution of 2-chlorobenzoxazole (12.78 g) in dry tetrahydrofuran (50 ml) was added, over 10 minutes, to a stirred, ice-cooled solution of ethanolamine (15.3 g) in dry tetrahydrofuran (400 ml). The mixture was heated at reflux overnight, cooled, and the solvent evaporated. The residue was partitioned between water (500 ml) and dichloromethane (500 ml), and the resulting white solid filtered off, washed with dichloromethane and dried in vacuo to afford the title compound m.p. 162°–4° C.

^{1}H NMR δ DMSO-d_6 3.3–3.8 (4H, complex); 5.0 (1H, br, exchanges with D_2O); 6.9–7.7 (4H, complex); 8.1 (1H, br, exchanges with D_2O).

PREPARATION 38

2-[N-(2-Benzoxazolyl)aminolethanol methanesulphonyl ester



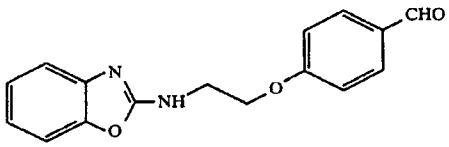
Methanesulphonyl chloride (4.9 g) was added dropwise to a stirred, ice-cooled solution of 2-[N-(2-benzoxazolyl-)amino]ethanol (6.23 g) and triethylamine (4.39 g) in dichloromethane (75 ml). The resulting mixture was stirred at 0° C. for 1.5h and then diluted with dichloromethane (200 ml), washed with water (2×200 ml), brine (200 ml) and dried. The dichloromethane layer was evaporated and the residue chromatographed on silica gel with 1.5% methanol in dichloromethane as eluent to give the title compound,

m.p. 96°–9° C..

^{1}H NMR δ $CDCl_3$3.0 (3H,s); 3.85 (2H,t); 4.5 (2H,t); 5.9 (1H,br, exchanges with D_2O); 7.0–7.5 (4H, complex).

PREPARATION 39

4-[2-(N-(2-Benzoxazolyl)amino)ethoxy]benzaldehyde

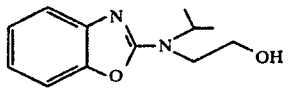


A mechanically stirred r'ixture of 2-[N-(2-benzoxazolyl-)amino]ethanol methanesulphonyl ester (5.77 g), 4-hydroxybenzaldehyde (2.81 g) and potassium carbonate (3.28 g) was heated at 80° C. overnight in dry DMF (250 ml). After cooling, the reaction mixture was concentrated in vacuo, diluted with water (500 ml) and extracted with ethyl acetate (3×300 ml). The combined ethyl acetate layers were washed with water (2×11). brine (11), dried and evaporated. The resulting solid was chromatographed on silica gel with 1.5% methanol in dichloromethane as eluent to afford the title compound, m.p. 103°–6° C.

^{1}H NMR δ $CDCl_3$ 3.9 (2H,t); 4.3 (2H,t); 6.4 (1H, br, exchanges with D_2O); 6.9–8.0 (8H, complex); 9.9 (1H,s).

PREPARATION 40

2-[N-Isopropyl-N-(2-benzoxazolyl)amino]ethanol

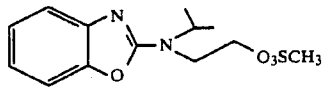


2-Chlorobenzoxazole (23.04 g) was added dropwise to an ice-cooled solution of 2-(isopropylamino)ethanol (15.45 g) and triethylamine (30.3 g) in tetrahydrofuran (500 ml). The mixture was stirred at room temperature for 30 minutes, then heated at reflux overnight before being cooled and evaporated. The residue was dissolved in dichloromethane (800 ml) and washed with saturated sodium bicarbonate solution (500 ml), water (3×11) brine (11), dried ($MgSO_4$), filtered and evaporated. The title compound was obtained as an oil following chromatography on silica gel using 1.5% methanol-dichloromethane as solvent.

^{1}H NMR δ ($CDCl_3$) 1.25 (6H,d); 3.6 (2H,t); 3.9 (2H,t); 4.5 (1H,m); 4.55 (1H, broad s, exchanges with D_2O); 6.95–7.50 (4H, complex).

PREPARATION 41

2-[N-Isopropyl-N-(2-benzoxazolyl)amino]ethanol methanesulchonyl ester.

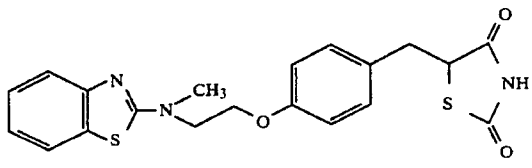


The title compound was prepared from 2-[N-isopropyl-N-(2-benzoxazolyl)amino]ethanol and methanesulphonyl chloride by a similar procedure to that described in Preparation 38.

^{1}H NMR δ ($CDCl_3$) 1.35 (6H,d); 3.0 (3H,s); 3.8 (2H,t); 4.3–4.7 (3H, complex); 6.9–7.5 (4H, complex).

EXAMPLE 1

5-(4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]-benzyl)-2,4-thiazolidinedione.



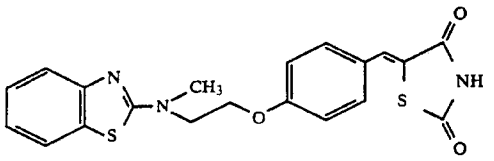
5-(4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]-benzylidene)-2,4-thiazolidinedione (2g) in dry 1,4-dioxan (70 ml) was reduced under hydrogen in the

presence of 10% palladium on charcoal (3 g) at ambient temperature and atmospheric pressure until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates were evaporated to dryness under vacuum. The title compound (m.p. 167°–8° C.) was obtained after crystallisation from methanol.

^{1}H NMR δ (DMSO-d_6) 2.9–3.4 (2H, complex); 3.25 (3H, s); 3.9 (2H, complex); 4.25 (2H, complex); 4.8 (1H, complex); 6.8–7.75 (8H, complex); 12.0 (1H, s, exchanges with D20).

EXAMPLE 2

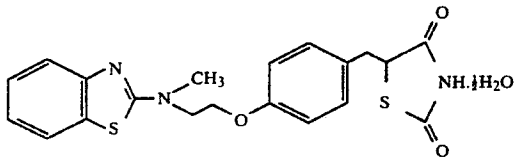
5-(4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]-benzylidene)-2,4-thiazolidinedione.



A solution of 4-[2-(N-methyl-N-(2-benzothiazolyl-)amino) ethoxy]benzaldehyde (1.9 g) and 2,4-thiazolidinedione (0.8 g) in toluene (100 ml) containing a catalytic quantity of piperidinium acetate was boiled under reflux in a Dean and Stark apparatus for 2 hours. The mixture was cooled and filtered and the filtered solid was dried to give the title compound (mp 219° C.). ^{1}H NMR δ (DMSO-d_6) 3.2 (3H, s); 3.9 (2H, t); 4.35 (2H, t); 6.8 –7.7 (10H, complex).

EXAMPLE 3

5-(4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxyl]-benzyl)-2,4-thiazolidinedione hemihydrate



5-(4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]-benzylidene)-2,4-thiazolidinedione (1.5 g) in dry 1,4-dioxan (80 ml) was reduced under hydrogen in the presence of 10% palladium on charcoal (2 g) at ambient temperature and atmospheric pressure until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates were evaporated to dryness under vacuum. The title compound (mp 147°–9° C.) was obtained after crystallisation from methanol.

^{1}H NMR δ (DMSO-d_6+D_2O)

3.1–3.5 (2H, complex); 3.3 (3H,s); 3.95 (2H, complex); 4.25 (2H, complex); 4.5 (1H, complex); 6.8–7.3 (8H, complex).

EXAMPLE 4

5-(4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]-benzylidene)-2,4-thiazolidinedione

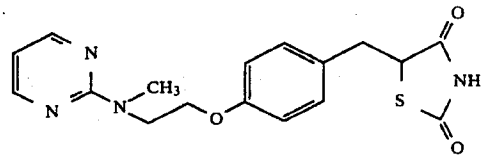
A solution of 4-[2-(N-methyl-N-(2-benzoxazolyl)amino) ethoxy]benzaldehyde (1.6 g) and 2,4-thiazolidinedione (0.63 g) in toluene (100 ml) containing a catalytic quantity of piperidinium acetate was boiled under reflux in a Dean and Stark apparatus for 2 hours. The mixture was cooled and filtered to give the title compound (mp 227°–9° C.).

^{1}H NMR δ (DMSO-d_6)

3.20 (3H, s); 3.90 (2H, t); 4.30 (2H, t); 6.9 –7.75 (10H, complex).

EXAMPLE 5

5-(4-[2-(N-Methyl-N-(2-pyrimidinyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione



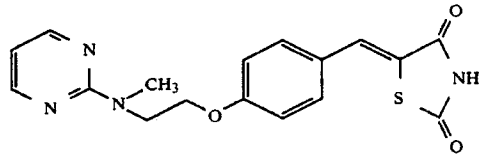
5-(4-[2-(N-Methyl-N-(2-pyrimidinyl)amino) ethoxy]-benzylidene)-2,4-thiazolidinedione (2.4 g) in dry 1,4-dioxan (150 ml) was reduced under hydrogen in the presence of 10% palladium on charcoal (3 g) until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates were evaporated to dryness under vacuum. The title compound (mp 150°–51° C.) was obtained after crystallisation from methanol.

^{1}H NMR δ (DMSO-d_6)

2.9–3.4 (2H, complex); 3.2 (3H, s); 3.9 (2H, complex); 4.2 (2H, complex); 4.9 (1H, complex); 6.6 (1H, t); 6.9 (2H, d); 7.2 (2H, d); 8.4 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 6

5-(4-[2-(N-Methyl-N-(2-pyrimidinyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione

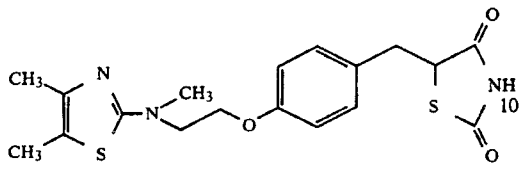


A solution of 4-[2-(N-methyl-N-(2-pyrimidinyl)amino) ethoxy]benzaldehyde (1.7 g) and 2,4-thiazolidinedione (0.7 g) in toluene (100 ml) containing a catalytic quantity of piperidinium acetate was boiled under reflux in a Dean and Stark apparatus for 2 hours. The mixture was cooled and filtered to give the title compound (mp 189°–90° C.).

^{1}H NMR δ (DMSO-d_6+D_2O) 3.2 (3H, s); 3.7–4.4 (4H, complex); 6.6 (1H, t); 7.1 (2H, d), 7.5 (2H, d); 7.7 (1H, s); 8.4 (2H, d).

EXAMPLE 7

5-(4-(2-(N-Methyl-N-[2-(4,5-dimethylthiazolyl)]amino) ethoxy]benzyl)-2,4-thiazolidinedione

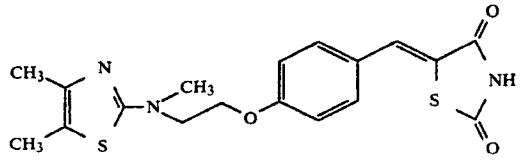


5-(4-[2-(N-Methyl-N-[2-(4,5-dimethylthiazolyl)]amino) ethoxy]benzylidene-2,4-thiazolidinedione (1.6 g) was dissolved in a mixture of methanol (50 ml) and dioxan (50 ml). Magnesium turnings (1.5 g) were added and the solution stirred until no more effervescence was observed. The mixture was added to water (300 ml), acidified (2M HCl) to form a solution, neutralised (saturated $NaHCO_3$ solution), filtered and dried. The solid was dissolved in dioxan (100 ml), adsorbed onto silica (20 g) and the title compound (m.p. 177° C.; MeOH) obtained following chromatography on silica-gel in 5% dioxan in dichloromethane.

^1H NMR δ (DMSO-d_6) 2.05 (3H, s); 2.15 (3H, s); 3.0 (3H, s); 3.0–3.4 (2H, complex); 3.8 (2H, t); 4.2 (2H, t); 4.85 (1H, complex); 6.9 (2H, d); 7.1 (2H, d); 12.0 (1H, broad s exchanges with D_2O).

EXAMPLE 8

2-(N-Methyl-N-2-(4,5-dimethylthiazolyl)]amino) ethoxy1benzylidene)-2,4-thiazolidinedione

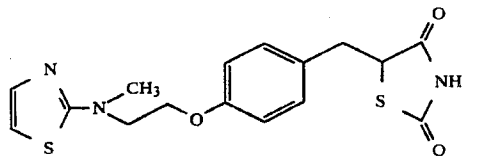


The title compound (m.p. 175° C.) was prepared by a similar procedure to that described in Example 4.

^1H NMR δ (DMSO-d_6) 2.0 (3H, s); 2.1 (3H, s); 3.0 (3H, s); 3.7 (2H, t); 4.25 (2H, t); 7.1 (2H, d); 7.55 (2H, d); 7.75 (1H, s); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 9

5-(4–2-(N-Methyl-N-(2-thiazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione

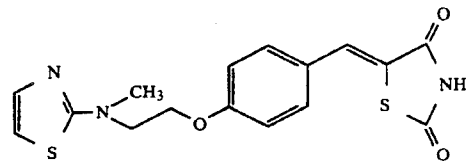


The title compound (m.p. 186° C.; MeOH) was prepared by an analogous procedure to that described in Example 7.

^1H NMR δ (DMSO-d_6) 3.0–3.4 (2H, complex); 3.1 (3H, s); 3.8 (2H, t); 4.2 (2H, t); 4.85 (1H, complex); 6.7–7.3 (6H, complex); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 10

5-(4-[2-(N-Methyl-N-(2-thiazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione

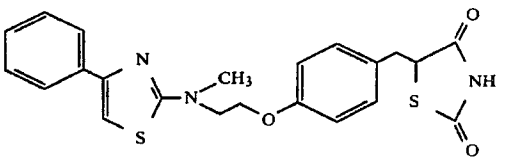


The title compound (m.p. 212° C.) was prepared by a similar procedure to that described in Example 4.

^1H NMR δ (DMSO-d_6) 3.1 (3H, s); 3.85 (2H, t); 4.3(2H, t); 6.75 (1H, d); 7.1–7.3 (3H, complex); 7.6 (2H, d); 7.75 (1H, s); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 11

5-[4-(2-(N-Methyl-N-(2-(4-phenylthiazolyl))amino) ethoxy)benzyl]-2,4-thiazolidinedione

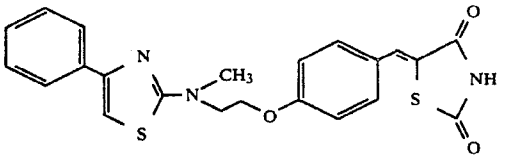


The title compound was obtained as a foam (m.p. 62°–65° C.) from 5-[4-(2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy)benzylidene]-2,4-thiazolidinedione (1.6 g) by a similar procedure to that described in Example 7.

^1H NMR δ (DMSO-d_6) 3.15 (3H, s); 3.0–3.4 (2H, complex); 3.9 (2H, t); 4.25 (2H, t); 4.85 (1H complex); 6.9 (2H, d); 7.1–7.45 (6H, complex); 7.85 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 12

5-(4–2-(N-Methyl-N-(2-(4-phenylthiazolyl))amino) ethoxy1benzylidene)-2,4-thiazolidinedione

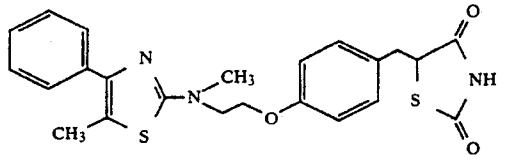


The title compound (m.p. 134° C.) was prepared from 4-[2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy]benzaldehyde by a similar procedure to that described in Example 4.

^1H NMR δ (DMSO-d_6) 3.2 (3H, s); 3.9 (2H, t); 4.35 (2H, t); 7.1–7.95 (11H, complex); 12.0 (1H broad s, exchanges with D_2O).

EXAMPLE 13

5-(4–2-(N-Methyl-N-[2-(4-phenyl-5-methylthiazolyl)-]amino)ethoxy]benzyl)-2,4-thiazolidinedione



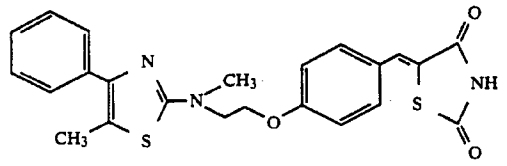
The title compound, obtained as a foam (m.p. 60°–62° C.), was prepared by an analogous procedure to that described in Example 7.

^{1}H NMR δ (DMSO-d_6) 2.35 (3H, s); 3.1 (3H, s); 3.0–3.4 (2H, complex); 3.8 (2H, t); 4.2 (2H, t); 4.85 (1H, complex);

6.9 (2H, d); 7.2 (2H, d); 7.25–7.5 (3H, complex); 7.65 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 14

5-(4[2-(N-Methyl-N-[2-(4-phenyl-5-methylthiazolyl)-]amino)ethoxy]benzylidene)-2,4-thiazolidinedione

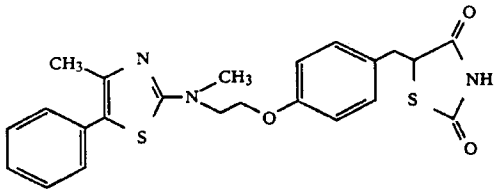


The title compound was prepared from 4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)]amino)ethoxy]benzaldehyde by a similar procedure to that described in Example 4, and was used in Example 13 without further purification.

^{1}H NMR δ (DMSO-d_6) 2.4 (3H, s); 3.1 (3H, s); 3.8 (2H, t); 4.35 (2H, t); 7.1–7.75 (10H, complex); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 15

5-(4-[2-(N-Methyl-N-[2-(4-methyl-5-phenylthiazolyl)-]amino)ethoxy]benzyl)-2,4-thiazolidinedione

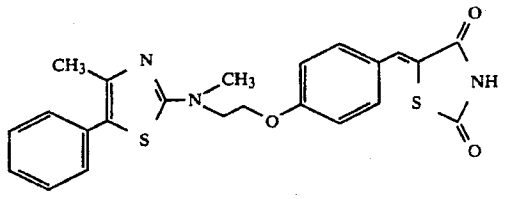


The title compound (m.p. 174° C.; MeOH) was prepared from 5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]amino)ethoxy]benzylidene)2,4-thiazolidinedione by an analogous procedure to that described in Example 7.

^{1}H NMR δ (DMSO-d_6) 2.3 (3H, s); 3.0–3.4 (2H, complex); 3.15 (3H, s); 3.85 (2H, t); 4.25 (2H, t); 4.85 (1H, complex); 6.95 (2H, d); 7.2 (2H, d); 7.45 (5H, complex); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 16

5-(4[2-(N-Methyl-N-2-(4-methyl-5-phenylthiazolyl)-]amino)ethoxy]benzylidene)-2,4-thiazolidinedione

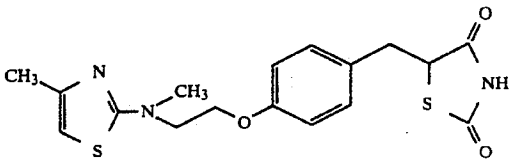


The title compound was prepared from 4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]amino)ethoxy]benzaldehyde by a similar procedure to that described in Example 4, and was used in Example 15 without further purification.

^{1}H NMR δ (DMSO-d_6) 2.3 (3H, s); 3.1 (3H, s); 3.85 (2H, t); 4.35 (2H, t); 7.15–7.75 (10H, complex); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 17

5-(4-[2-(N-Methyl-N-2-(4-methylthiazolyl)]amino)-ethoxy]benzyl)-2,4-thiazolidinedione

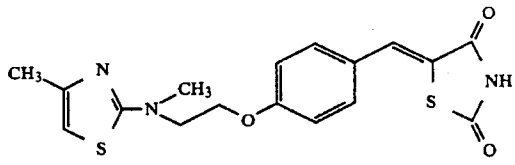


The title compound, was prepared from 5-(4-[2-(N-methyl -N-[2-(4-methylthiazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione as a foam (m.p. 121° C.), by a similar procedure to that described in Example 7.

^{1}H NMR δ (DMSO-d_6) 2.1 (3H, s); 3.0–3.4 (2H, complex); 3.1 (3H, s); 3.75 (2H, t); 4.15 (2H, t); 4.85 (1H, complex); 6.3 (1H, s); 6.9 (2H, d); 7.2 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 18

5-(4–2-(N-Methyl-N-[2-(4-methylthiazolyl)]amino) ethoxy]benzylidene)-2,4-thiazolidinedione

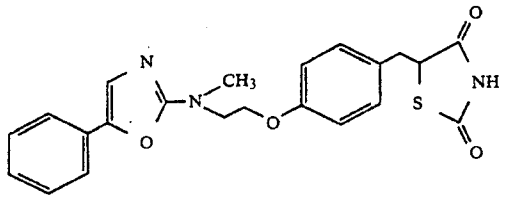


The title compound was prepared from 5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)]amino)ethoxy]benzaldehyde by a similar procedure to that described in Example 4, and was used in the Example 17 without further purification.

^{1}H NMR δ (DMSO-d_6) 2.1 (3H, s); 3.1 (3H, s); 3.85 (2H, d); 4.3 (2H, d); 6.3 (1H, s); 7.15 (2H, d); 7.6 (2H, d); 7.75 (1H, s); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 19

5-[4-(2-(N-Methyl-N-[2-(5-phenyloxazolyl)]amino) ethoxy)benzyl]2,4-thiazolidinedione

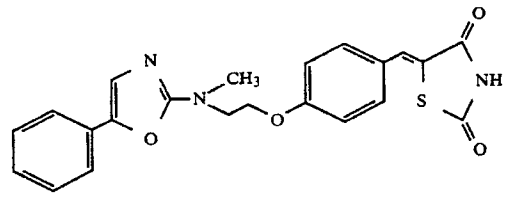


The title compound (m.p. 200° C., MeOH)) was prepared from 5-[4-(2-(N-methyl-N-[2-(5-phenyloxazolyl)-]amino ethoxy)benzylidene]-2,4-thiazolidinedione by a similar procedure to that described in Example 7.

^{1}H NMR δ (DMSO-d_6) 3.0–3.4 (2H, complex); 3.15 (3H, s); 3.8 (2H, t); 4.2 (2H, t); 4.85 (1H, complex); 6.9 (2H, d); 7.1–7.4 (6H, complex); 7.5 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 20

5-(4-[2-(N-Methyl-N-[2-(5-phenyloxazolyl)]amino) ethoxy]benzylidene)-2,4-thiazolidinedione

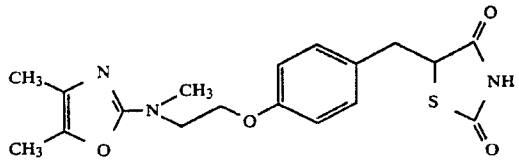


The title compound (m.p. 191° C.) was prepared from 4-[2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino) ethoxy]benzaldehyde by an analogous procedure to that described in Example 4.

^{1}H NMR δ (DMSO-d_6) 3.2 (3H, s); 3.8 (2H, t); 4.35 (2H, t); 7.1–7.7 10H, complex); 7.8 (1H, s); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 21

5-(4[2-(N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino) ethoxy]benzyl)-2,4-thiazolidinedione

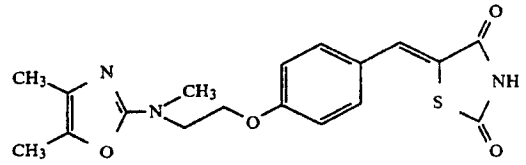


5-(4-[2-(N-Methyl-N-[2-(4,5-dimethyloxazolyl)-]amino)ethoxy]benzylidene)-2,4-thiazolidinedione (1.2 g) in dry 1,4-dioxan (100 ml) was reduced under hydrogen in the presence of 10% Palladium on charcoal (2.5 g) until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates evaporated to dryness under vacuum. The title compound was obtained as a foam (m.p. 53°–54° C.) following chromatography on silica-gel in 1% methanol in dichloromethane.

^{1}H NMR δ (DMSO-d_6) 1.85 (3H, s); 2.05 (3H, s); 3.0 (3H, s); 3.0–3.4 (2H, complex); 3.65 (2H, t); 4.1 (2H, t); 4.85 (1H, complex); 6.85 (2H, d); 7.15 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 22

5-(4[2-(N-Methyl-N-2-(4,5-dimethyloxazoly)]amino)e-thoxy]benzylidene-2,4-thiazolidinedione



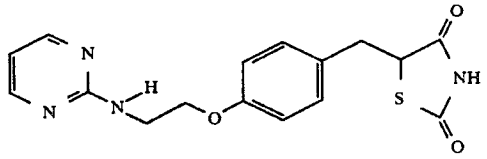
The title compound (softens at 149° C.) was prepared by a similar procedure to that described in Example 4.

^{1}H NMR δ (DMSO-d_6) 1.85 (3H, s); 2.05 (3H, s); 3.0 (3H, s); 3.7 (2H, t); 4.25 (2H, t); 7.1 (2H, d); 7.5 (2H, d); 7.75 (1H, s);

12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 23

5–4-(2-(2-Pvrimidinylamino)ethoxy)benzv11–2,4-thiazolidinedione

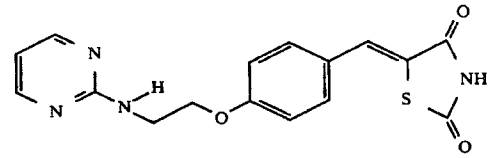


A mixture of 5-[4-(2-(2-pyrimidinylamino)ethoxy) benzylidene]-2,4-thiazolidinedione (3 g) and 10% palladium on charcoal (9 g) in DMF (70 ml) was stirred under a pressure of 200 psi of hydrogen until hydrogen uptake ceased. The mixture was filtered through diatomaceous earth, and the filter pad washed exhaustively with DMF. The combined filtrates were evaporated to dryness and the title compound (m.p. 173° C.) obtained following recrystallization from methanol.

^{1}H NMR δ (DMSO-d_6) 3.0–3.4 (2H, complex); 3.65 (2H, complex); 4.1 (2H, t); 4.85 (1H, complex); 6.6 (1H, t); 6.85 (2H, d); 7.15 (2H, d); 7.25 (1H, t, exchanges with D_2O); 8.3 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 24

5-[4-(2-(2-Pyrimidinylamino)ethoxy)benzylidenel-2,4-thiazolidinedione



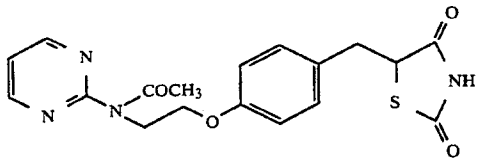
The title compound (m.p. 234° C.) was obtained from 4-[2-(2-pyrimidinylamino)ethoxy]benzaldehyde and 2,4-thiazolidindione, by an analogous procedure to that described in Example 6.

^{1}H NMR δ (DMSO-d_6) 3.65 (2H, complex); 4.2 (2H,t); 6.6 (1H, t); 7.0–7.6 (5H, complex, one proton

changes with D_2O); 7.7 (1H, s); 8.3 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 25

5-(4-[2-(N-Acetyl-N-(2-pyrimidinyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione

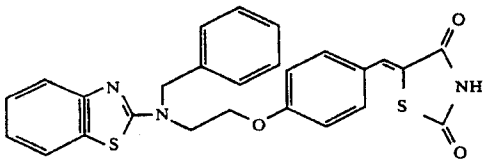


A stirred solution of 5-[4-(2-(2-pyrimidinylamino) ethoxy)benzyl]-2,4-thiazolidinedione (800mg) in acetic anhydride (15 ml) and 1,4-dioxan (5 ml) was boiled under reflux for 3 hours. After cooling, the mixture was added to water (300 ml), neutralized (sodium bicarbonate) and extracted with dichloromethane (3×200 ml). The organic extracts were washed with brine (100 ml), dried ($MgSO_4$), filtered and evaporated to dryness. Chromatography on silica-gel in dichloromethane of the residual oil afforded the title compound (m.p. 137° C.).

^1H NMR δ (DMSO-d_6) 2.3 (3H, s); 2.93.4 (2H, complex); 4.15 (2H,t); 4.35 (2H, t); 4.85 (1H, complex); 6.7 (2H,d); 7.1 (2H, d); 7.35 (1H, t); 8.8 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 26

5-(4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy) benzylidene)-2,4-thiazolidinedione

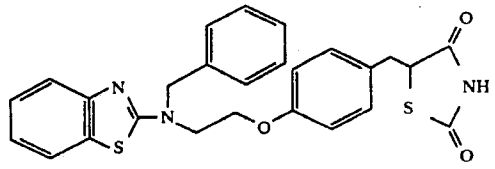


4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy) benzaldehyde (3 g) and 2,4-thiazolidinedione (1 g) were dissolved in toluene (200 ml) containing piperidine (0.2 ml) and benzoic acid (0.2 g) and heated to reflux for 4 h. in a Dean and Stark apparatus. On cooling, the solution was concentrated under vacuum to 50% of its volume and the title compound, which crystallised, was collected by filtration and dried in vacuo (m.p. 185°–188° C.). It was used in Example 27 without further purification.

^1H NMR δ (DMSO-d_6) 4.0 (2H, t); 4.4 (2H, t); 4.9 (2H, s); 7.1–7.9 (14H, complex); 12–13 (1H, broad s, exchanges with D_2O).

EXAMPLE 27

5-(4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy) benzyl)-2,4-thiazolidinedione

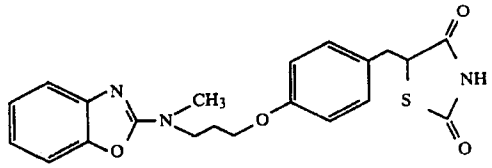


5-(4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy) benzylidene)-2,4-thiazolidinedione (2.4 g) in dioxan (150 ml) was hydrogenated in the presence of 10% palladium-charcoal (4.8 g) for 3 h. at room temperature and atmospheric pressure. A further portion of catalyst (2.4 g) was added and the hydrogenation continued for a total of 20 h. The mixture was filtered through diatomaceous earth and the solvent was evaporated. The residue was chromatographed on silica gel with 3% methanol-dichloromethane as eluant to afford the title compound as a foam, which collapsed at 78° C.

^1H NMR δ ($CDCl_3$) 3.1 (1H, dd); 3.4 (1H, dd); 4.0 (2H, t); 4.25 (2H, t); 4.5 (1H, dd); 4.9 (2H, s); 6.8–7.6 (13H, m); 8.3 (1H, broad s, exchanges with D_2O).

EXAMPLE 28

5-(4–3-(N-Methyl-N-(2-benzoxazolyl)amino)propoxy]-benzyl)-2,4-thiazolidinedione

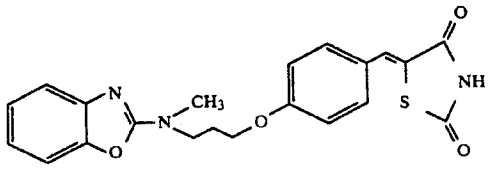


The title compound (m.p. 171°–3° C.; ethanol) was prepared from 5-(4-[3-(N-methyl-N-(2-benzoxazolyl-)amino)propoxy]benzylidene)-2–4-thiazolidinedione by a similar procedure to that described in Example 1.

^1H NMR δ) (DMSO - d_6) 2.0–2.35 (2H, complex); 2.9–3.6 (2H, complex); 3.2 (3H, s); 3.7 (2H, t); 4.2 (2H, t); 4.9 (1H, complex); 6.8–7.4 (8H, complex); 12–12.5 (1H, broad s, exchanges with D_2O).

EXAMPLE 29

4-[3-(N-Methyl-N-(2-benzoxazolyl)amino)propoxy]-benzylidene)-2,4-thiazolidinedione

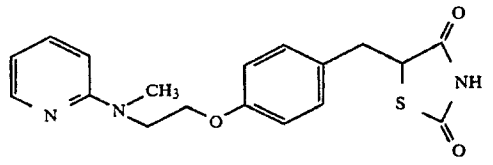


The title compound (m.p. 202°–204° C.) was prepared from 4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propoxy]benzaldehyde (5.3 g) and 2,4-thiazolidinedione (2.2 g) by a similar procedure to that described in Example 4.

^{1}H NMR δ (DMSO - d_6) 2.0–2.35 (2H, complex); 3.15 (3H, s); 3.7 (2H, t); 4.2 (2H, t); 7.0–7.7 (8H, complex); 7.8 (1H, s); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 30

5-(4–2-(N-Methyl-N-(2-ovridyl)amino)ethoxy1benzyl)2,4-thiazolidinedione

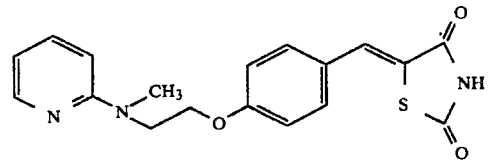


The title compound (m.p. 153°–5° C.; MeOH) was obtained from 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione by a similar procedure to that described in Example 1.

^{1}H NMR δ (DMSO - d_6) 2.9–3.4 (2H, complex); 3.1 (3H, s); 3.9 (2H, t); 4.15 (2H, t); 4.8 (1H, complex); 6.5–6.85 (2H, complex); 6.8 (2H, d); 7.2 (2H, d); 7.5 (1H, complex); 8.1 (1H, d); 12.05 (1H, broad s, exchanges with D_2O).

EXAMPLE 31

5-(4-[2-(N-Methyl-N-(2-cvridyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione

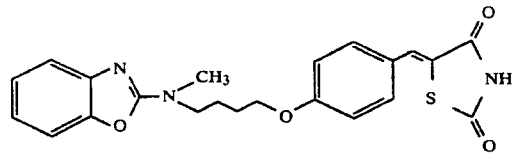


The title compound (m.p. 177°–9° C.) was obtained from 4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzaldehyde (3.2 g) and 2,4-thiazolidinedione (1.1 g) by a similar procedure to that described in Example 4.

^{1}H NMR δ (DMSO-D_2O) 3.1 (3H, s); 3.9 (2H, t); 4.2 (2H, t); 6.4–7.5 (7H, complex); 7.7 (1H, s); 8.1 (1H, d)

EXAMPLE 32

5-(4-[4-(N-Methyl-N-(2-benzoxazolyl)amino)butoxy]-benzylidene)-2,4-thiazolidinedione.

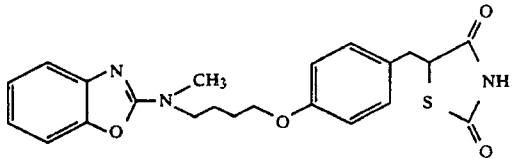


The title compound (m.p. 168° C.; was prepared from 4-[4-(N-methyl-N-(2-benzoxazolyl)amino)butoxy]benzaldehyde (3.5 g) and 2,4-thiazolidinedione (1.4 g) by a similar procedure to that described in Example 4.

^{1}H NMR δ DMSO-$d_6$1.70 (4H, complex); 3.10 (3H, s); 3.25 (1H, exchanges with D_2O); 3.50 (2H, complex); 4.05 (2H, complex); 6.90–7.60 (8H, complex); 7.70 (1H, s).

EXAMPLE 33

5(4-[4-(N-Methyl-N-(2-benzoxazolyl)amino)butoxy]-benzyl)-2,4-thiazolidinedione

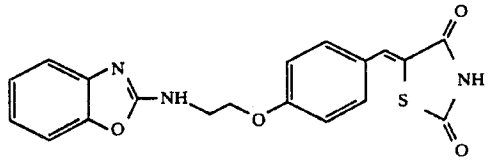


The title compound (m.p. 112° C., ethanol-hexane) was prepared from 5-(4-[4-(N-methyl-N-(2-benzoxazolyl-)amino)butoxy]benzylidene)-2,4-thiazolidinedione by a similar procedure to that described in Example 1.

^{1}H NMR δ $CDCl_3$1.85 (4H, complex); 3.10 (1H, complex); 3.15 (3H,s); 3.40 (1H,dd); 3.60 (2H,t); 4.00 (2H,t); 4.50 (1H,dd); 6.80–7.40 (8H, complex); 9.30 (1H, br, exchanges with D_2O).

EXAMPLE 34

5-(4-[2-(N-(2-Benzoxazolyl)amino)ethoxy]benzylidene)2,4-thiazolidinedione

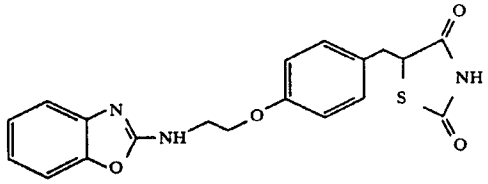


The title compound (m.p. 242°–5° C.) was prepared from 4-[2-(N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde (5.18 g) and 2,4-thiazolidinedione (2.36 g) by a similar procedure to that described in Example 4.

^{1}H NMR δ DMSO-$d_6$3.80 (2H,t); 4.35 (2H,t); 7.00–8.00 (9H, complex); 8.20 (1H, br, exchanges with D_2O); 13.5 (1H, br, exchanges with D_2O).

EXAMPLE 35

5-(4-[2-(N-(2-Benzoxazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione

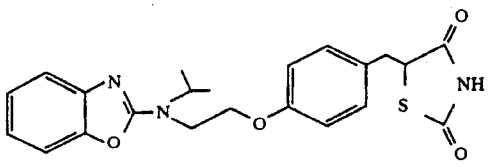


The title compound (m.p. 202°–3° C.; dichloromethane) was prepared from 5-(4-[2-(N-(2-benzoxazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione (6.1 g) by a similar procedure to that described in Example 1.

^{1}H NMR δ DMSO-$d_6$3.10 (1H,dd); 3.30 (1H,dd) 3.70 (2H, complex); 4.15 (2H,t); 4.85 (1H,dd); 6.80–7.50 (8H, complex); 8.15 (1H, complex; exchanges with D_2O); 12.00 (1H, br, exchanges with D_2O).

EXAMPLE 36

5-(4[2-(N-Isopropyl-N-(2-benzoxazolyl)amino)ethoxy]-benzyl)-2,4-thiazolidinedione.



Sodium hydride (60% dispersion in mineral oil, 0.93 g) was added portionwise to a stirred solution of 5-(4-hydroxybenzyl)-2,4-thiazolidinedione (2.45 g in dry DMF (50 ml)) at room temperature under a nitrogen atmosphere. The mixture was stirred for 1 hour prior to the addition of a solution of 2-[N-isopropyl-N-(2-benzoxazolyl)amino]ethanol methanesulphonyl ester (3.3 g) in dry DMF (60 ml). After stirring at room temperature for a further hour, the mixture was heated at 80° C. for 21 hours, then cooled, diluted with water (1l) and acidified to pH 6.5 with hydrochloric acid. The resulting suspension was extracted with ethyl acetate (2×500 ml), and the combined ethyl acetate layers washed with water (3×1l), brine (1l), dried ($MgSO_4$) and evaporated. The residual oil was chromatographed on silica gel with 1.5% methanol-dichloromethane as solvent to afford the title compound as a foam (m.p. 66° C.).

^1H NMR δ ($CDCl_3$) 1.35 (6H,d); 3.1 (1H, dd); 3.4 (1H, dd); 3.8 (2H,t); 4.15 (2H, complex); 4.35–4.65 (2H, complex); 6.85–7.4 (8H, complex); and 9.15 (1H, broad s,; exchanges With D_2O)

DEMONSTRATION OF EFFICACY OF COMPOUNDS

Obese Mice, Oral Glucose Tolerance Test

C57bl/6 obese (ob/ob) mice were fed on powdered oxoid diet. After at least one week, the mice continued on a powdered oxoid diet or were fed powdered oxoid diet containing the test compound. After 8 days on the supplemented diet all of the mice were fasted for 5 hours prior to receiving an oral load of glucose (3 g/kg). Blood samples for glucose analysis were taken 0, 45, 90 and 135 minutes after glucose administration and the results appear below as the percentage reduction in area under the blood glucose curve where test compound treated groups are compared with the control groups. 7 mice were used for each treatment.

EXAMPLE NO:	LEVEL IN DIET (μmol kg^{-1} of DIET)	% REDUCTION IN AREA UNDER BLOOD GLUCOSE CURVE
1	100	51
2	300	30
3	10	39
4	300	30
5	100	40
7	50	47
9	100	58
11	100	34
13	100	37
15	100	39
17	100	34
19	30	22
21	30	33
24	30	15
25	30	19
27	300	56

-continued

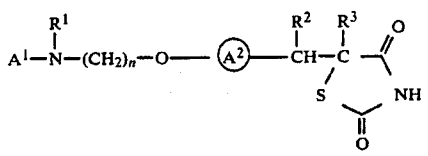
EXAMPLE NO:	LEVEL IN DIET (μmol kg^{-1} of DIET)	% REDUCTION IN AREA UNDER BLOOD GLUCOSE CURVE
29	300	32
33	300	25
35	100	44
36	100	20

Toxicology

No toxicological effects were indicated for any of the compounds of the invention in any of the abovementioned tests.

I claim:

1. A compound of formula (I):



(I)

or a tautomeric form thereof and/or pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted, single ring aromatic heterocyclyl group having 4 to 7 ring atoms and comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen, the substituents for the heterocyclyl group being up to 4 substituents selected from the group consisting of: C_{1-12} -alkyl, C_{1-12}-alkoxy, aryl and halogen or any two substituents on adjcent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted;

R^1 represents a hydrogen atom, a C_{1-12}-alkyl group, a C_{1-6} alkylcarbonyl group, an aryl-C_{1-12}-alkyl group the aryl moiety being substituted or unsubstituted, or a substituted or unsubstituted aryl group;

any aryl group being phenyl or naphthyl optionally substituted with up to five groups selected from halogen, C_{1-12}-alkyl, phenyl, C_{1-12}-alkoxy, halo-C_{1-12}-alkyl, hydroxy, amino, nitro, carboxy, C_{1-12}-alkylcarbonyloxy, or a C_{1-12}-alkylcarbonyl group;

Rhu 2 and R^3 each represent hydrogen, or R^2 and R^3 together represent a bond;

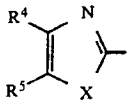
A^2 represents a benzene ring having three optional substituents which may be selected from halogen, substituted or unsubstituted alkyl or alkoxy; substituents for the alkyl group being selected from the groups consisting of halogen, C_{1-12}-alkyl, phenyl, C_{1-12}-alkoxy, halo-C_{1-12}-alkyl, hydroxy, amino, nitro, carboxy, C_{1-12}-alkoxycarbonyl, C_{1-12}-alkoxycarbonyl-C_{1-12}-alkyl, C_{1-12}-alkylcarbonyloxy, or C_{1-12}-alkylcarbonyl; and

n represents an integer in the range of from 2 to 6.

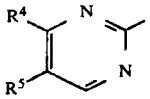
2. A compound according to claim 1, wherein A^1 represents a substituted or unsubstituted, single or fused ring aromatic heterocyclyl group comprising up to 4 hetero atoms in the ring selected from oxygen, sulphur or nitrogen.

3. A compound according to claim 1, wherein A^1 represents a moiety of formula (a), (b) or (c):

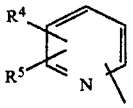
(a)



(b)



(c)



wherein:

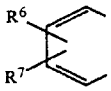
R^4 and R^5 each independently represents a hydrogen atom, an alkyl group or a substituted or unsubstituted aryl group or when R^4 and R^5 are each attached to a carbon atom, then R^4 and R^5 together with the carbon atoms to which they are attached form a benzene ring wherein each carbon atom represented by R^4 and R^5 together may be substituted or unsubstituted; and in the moiety of formula (a)

X represents oxygen or sulphur.

4. A compound according to claim **3**, wherein R^4 and R^5 each independently represent hydrogen, alkyl or a substituted or unsubstituted phenyl group.

5. A compound according to claim **3**, wherein R^4 and R^5 together represent a moiety of formula (d):

(d)

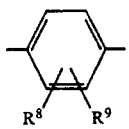


wherein R^6 and R^7 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

6. A compound according to claim **5**, wherein R^6 and R^7 both represent hydrogen.

7. A compound according to claim **1**, wherein A^2 represents a moiety of formula (e):

(e)

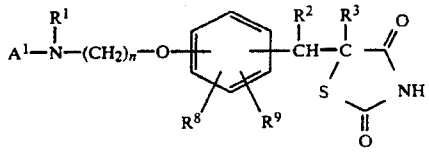


wherein R^8 and R^9 each independently represent hydrogen, halogen, suostituted or unsubstituted alkyl or alkoxy.

8. A compound according to claim **7**, wherein R^8 and R^9 each represent hydrogen.

9. A compound according to claim **1**, of formula (II):

(II)



or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein A^1, R^1, R^2, R^3 and n are as defined in relation to formula (I) in claim **1** and R^8 and R^9 are as defined in relation to formula (e) in claim **7**.

10. A compound according to claim **1**, wherein n represents an integer 2 or 3.

11. A compound according to claim **1**, wherein R^1 represents a methyl group.

12. A compound according to claim **1**, selected from the group consisting of:

5-(4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]-benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]-benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-pyrimidinyl)amino)ethoxy]-benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-pyrimidinyl)amino)ethoxy]-benzylidene)-2,4-thiazolidinedione;

5-(4-(2-(N-methyl-N-[2-(4,5-dimethylthiazolyl)-]amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4,5-dimethylthiazolyl)-]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-thiazolyl)amino)ethoxy]benzyl) -2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-thiazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-[4-(2-(N-methyl-N-(2-(4-phenylthiazolyl))amino) ethoxy)benzyl]-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-(4-phenylthiazolyl))amino) ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)-]amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)-]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)-]amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)-]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

b 5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)-]amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)]amino) ethoxy]benzylidene)-2,4-thiazolidinedione;

5-[4-(2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino) ethoxy)benzyl]-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino) ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4,5-dimethyloxazolyl)-]amino) ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4,5-dimethyloxazolyl)-]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-[4-(2-(2-pyrimidinylamino)ethoxy)benzyl]-2,4-thiazolidinedione;

5-[4-(2-(2-pyrimidinylamino)ethoxy)benzylidene]-2,4-thiazolidinedione;

5-(4-[2-(N-acetyl-N-(2-pyrimidinyl)amino)ethoxy]-benzyl) -2,4-thiazolidinedione;

5-(4-(2-(N-(2-benzothiazolyl)-N-benzylamino)e-thoxy) benzylidene)-2,4-thiazolidinedione;

5-(4-(2-(N-(2-benzothiazolyl)-N-benzylamino)e-thoxy) benzyl)-2,4-thiazolidinedione;

5-(4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propox-y]benzyl)-2,4-thiazolidinedione;

5-(4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propox-y]benzy lidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]ben-zyl)-2,4-thiazolidinedione;

5-(4 [2-(N-methyl-N-(2-pyridyl)amino)ethoxy]ben-zylidene)-2,4-thiazolidinedione;

5-(4-[4-(N-methyl-N-(2-benzoxazolyl)amino)butoxy]-benzylidene)-2,4-thiazolidinedione;

5-(4-[4-(N-methyl-N-(2-benzoxazolyl)amino)butoxy]-benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-(2-benzoxazolyl)amino)ethoxy]ben-zylidene)2,4-thiazolidinedione;

5-(4-[2-(N-(2-benzoxazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; and

5-(4-[2-(N-isopropyl-N-(2-benzoxazolyl)amino)e-thoxy]benzyl)-2,4-thiazolidinedione; or a tauto-meric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

13. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

14. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]ben-zylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

15. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

16. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]ben-zylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

17. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-(2-pyrimidinyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

18. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-(2-pyrimidinyl)amino)ethoxy]ben-zylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

19. A compound according to claim **1** being 5-(4-(2-(N-methyl-N-[2-(4,5-dimethylthiazolyl)]amino)ethoxy]-benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

20. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-[2-(4,5-dimethylthiazolyl)]amino)ethoxy]-benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

21. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-(2-thiazolyl)amino)ethoxy]benzyl)2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

22. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-(2-thiazolyl)amino)ethxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

23. A compound according to claim **1** being 5-[4-(2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy)ben-zyl]-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and-/or a pharmaceutically acceptable solvate thereof.

24. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy]ben-zylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof

25. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)]amino)e-thoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

26. A compound according to claim **1** being **5**-(4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)]amino)e-thoxy]benzylidene)-2,4-thiazolidinedine; or a tauto-meric form thereof and/or a pharmaceutically accept-able salt thereof and/or a pharmaceutically acceptable solvate thereof

27. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]amino)e-thoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

28. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]amino)e-thoxy]benzylidene)-2,4-thiazolidinedione; or a tauto-meric form thereof and/or a pharmaceutically accept-able salt thereof and/or a pharmaceutically acceptable solvate thereof.

29. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)]amino)ethoxy]ben-zyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and-/or a pharmaceutically acceptable solvate thereof.

30. A compound according to claim **1** being 5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)]amino)ethoxy]ben-zylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

31. A compound according to claim **1** being 5-[4-(2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino)ethoxy)ben-zyl]-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and-/or a pharmaceutically acceptable solvate thereof.

32. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

33. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-[2-(4,5-dimethyloxazolyl)]amino)ethoxy]-benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

34. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-[2-(4,5-dimethyloxazolyl)]amino)ethoxy]-benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

35. A compound according to claim 1 being 5-[4-(2-(2-pyrimidinylamino)ethoxy)benzyl]-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

36. A compound according to claim 1 being 5-[4-(2-(2-pyrimidinylamino)ethoxy)benzylidene]-2,4thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

37. A compound according to claim 1 being 5-(4-[2-(N-acetyl-N-(2-pyrimidinyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically accepta,ble solvate thereof.

38. A compound according to claim 1 being 5-(4-(2-(N-(2-benzothiazolyl)-N-benzylamino)ethoxy)benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

39. A compound according to claim 1 being 5-(4-(2-(N-(2-benzothiazolyl)-N-benzylamino)ethoxy)benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

40. A compound according to claim 1 being 5-(4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

41. A compound according to claim 1 being 5-(4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propoxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

42. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl)2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

43. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

44. A compound according to claim 1 being 5-(4-[4-(N-methyl-N-(2-benzoxazolyl)amino)butoxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

45. A compound according to claim 1 being 5-(4-[4-(N-methyl-N-(2-benzoxazolyl)amino)butoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

46. A compound according to claim 1 being 5-(4-[2-(N-(2-benzoxazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

47. A compound according to claim 1 being 5-(4-[2-(N-(2-benzoxazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

48. A compound according to claim 1 being 5-(4-[2-(N-isopropyl-N-(2-benzoxazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and-/or a pharmaceutically acceptable solvate thereof.

49. A compound according to claim 1, wherein A^1 represents a substituted or unsubstituted single ring aromatic heterocyclyl group having 5 or 6 ring atoms.

50. A compound according to claim 1, wherein A^1 represents a substituted or unsubstituted thiazolyl, oxazolyl, pyridyl or pyrimidinyl group.

51. A compound according to claim 1, wherein A^1 represents a substituted or unsubstituted oxazolyl, pyridyl or pyrimidinyl group.

52. A pharmaceutical composition comprising a non-toxic effective amount of the compound of formula (I) according to claim 1, or a tautomeric form thereof or a pharmaceutically acceptable salt thereof or pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

53. A method for the treatment and/or prophylaxis of hyperglycaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, to a hyperglycaemic human or non-human mammal in need thereof.

54. A method for the treatment of hyperlipidaemia in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, to a hyperlipidaemic human or non-human mammal in need thereof.

55. A method for the treatmetn and/or prophylaxis of diseases selected from the group consisting of hyperglycaemia and hyperlipidaemia in a human or a non-human mammal which comprises administering to said human or non-human mammal in need thereof, an effective, non-toxic, amount of a compound of formula (I) according to claim 1, or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,002,953

DATED : March 26, 1991

INVENTOR(S) : Richard M. Hindley, Surrey, England

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 1, Col. 38, line 35, "adjcent" should be --adjacent--;

line 49, all of line containing "alkylcarbonyloxy, or a C_{1-12}-alkylcarbonyl group;" should be replaced by the following:

-- alkoxycarbonyl, C_{1-12}-alkoxycarbonyl-C_{1-12} alkyl, C_{1-12}-alkylcarbonyloxy, or a C_{1-12}-alkylcarbonyl group;--;

line 50, "Rhu-2" should be --R^2--;

Claim 7, Col. 39, line 62, "suostituted" should be --substituted--;

Claim 12, Col. 40, line 55, delete "b";

Col. 41, line 12, "benzy lidene" should be --benzylidene--;

Col. 41, line 15, "5-(4 [" should be --5-(4-[--;

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,002,953

DATED : March 26, 1991

INVENTOR(S) : Richard M. Hindley

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 22, Col. 42, line 13, ")ethxy]" should be --)ethoxy]--;

Signed and Sealed this

Twenty-fifth Day of August, 1992

Attest:

Attesting Officer

DOUGLAS B. COMER

Acting Commissioner of Patents and Trademarks

UNITED STATES DISTRICT COURT

DISTRICT OF NEW JERSEY

SMITHKLINE BEECHAM PLC, an English Public Limited Company, SB PHARMCO PUERTO RICO INC., a Puerto Rican Corporation, and SMITHKLINE BEECHAM CORPORATION, a Pennsylvania Corporation, Plaintiffs, v. TEVA PHARMACEUTICALS INDUSTRIES LTD., an Israeli Company, TEVA PHARMACEUTICALS USA, INC., a Delaware Corporation, Defendants.	Civil Action No. _____ **SUMMONS**

TO: Teva Pharmaceuticals USA, Inc.
1090 Horsham Road
North Wales, Pennsylvania 19454-1090.

YOU ARE HEREBY SUMMONED and required to file with the Clerk of this Court and serve upon PLAINTIFF'S ATTORNEY:

Douglas S. Eakeley, Esq.
Lowenstein Sandler PC
65 Livingston Avenue
Roseland, New Jersey 07068

an answer to the complaint which is herewith served upon you, within 20 days after service of this summons upon you, exclusive of the day of service. If you fail to do so, judgment by default will be taken against you for the relief demanded in the complaint.

CLERK _____ DATE _____

BY DEPUTY CLERK _____

16212/2
01/20/2004 1498801.01

RETURN OF SERVICE

Service of the Summons and Complaint was made by me	DATE
NAME OF SERVER	TITLE

Check one box below to indicate appropriate method of service

☐ Served personally upon the defendant. Place where served _____

_____

☐ Left copies thereof at the defendant's dwelling house or usual place of abode with a person of suitable age and discretion then residing therein.
Name of person with whom the summons and complaint were left: _____

☐ Return unexecuted: _____

_____

_____

☐ Other (specify). _____

_____

STATEMENT OF SERVICE FEES

TRAVEL	SERVICES	TOTAL

DECLARATION OF SERVER

I declare under penalty of perjury under the laws of the United States of America that the foregoing information contained in the Return of Service and Statement of Services Fees is true and correct.

Executed on _____ _____
Date Signature of Server

_____
Address of Server

UNITED STATES DISTRICT COURT

DISTRICT OF NEW JERSEY

SMITHKLINE BEECHAM PLC, an English Public Limited Company, SB PHARMCO PUERTO RICO INC., a Puerto Rican Corporation, and SMITHKLINE BEECHAM CORPORATION, a Pennsylvania Corporation, Plaintiffs, v. TEVA PHARMACEUTICALS INDUSTRIES LTD., an Israeli Company, TEVA PHARMACEUTICALS USA, INC., a Delaware Corporation, Defendants.	Civil Action No. _____ **SUMMONS**

TO: Teva Pharmaceuticals Industries Ltd.
5 Basel St. Petach Tikva 49131, Israel.

YOU ARE HEREBY SUMMONED and required to file with the Clerk of this Court and serve upon PLAINTIFF'S ATTORNEY:

Douglas S. Eakeley, Esq.
Lowenstein Sandler PC
65 Livingston Avenue
Roseland, New Jersey 07068

an answer to the complaint which is herewith served upon you, within 20 days after service of this summons upon you, exclusive of the day of service. If you fail to do so, judgment by default will be taken against you for the relief demanded in the complaint.

CLERK _____ DATE _____

BY DEPUTY CLERK _____

16212/2
01/20/2004 1498807.01

RETURN OF SERVICE

Service of the Summons and Complaint was made by me	DATE
NAME OF SERVER	TITLE

Check one box below to indicate appropriate method of service

☐ Served personally upon the defendant. Place where served _____

_____

☐ Left copies thereof at the defendant's dwelling house or usual place of abode with a person of suitable age and discretion then residing therein.
Name of person with whom the summons and complaint were left: _____

☐ Return unexecuted: _____

_____

_____

☐ Other (specify). _____

_____

STATEMENT OF SERVICE FEES

TRAVEL	SERVICES	TOTAL

DECLARATION OF SERVER

I declare under penalty of perjury under the laws of the United States of America that the foregoing information contained in the Return of Service and Statement of Services Fees is true and correct.

Executed on _____ _____
Date Signature of Server

_____
Address of Server

CIVIL COVER SHEET

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS

SMITHKLINE BEECHAM PLC, an English Public Limited Company;

SB PHARMCO PUERTO RICO INC., a Puerto Rican Corporation;

SMITHKLINE BEECHAM CORPORATION, a Pennsylvania Corporation

(b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF: Middlesex, England.
(EXCEPT IN U.S. PLAINTIFF CASES)

DEFENDANTS

TEVA PHARMACEUTICALS INDUSTRIES LTD., an Israeli Company;

TEVA PHARMACEUTICALS USA, INC., a Delaware Corporation.

COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

(c) ATTORNEYS (FIRM NAME, ADDRESS, AND TELEPHONE NUMBER)

(See attachment).

ATTORNEYS (IF KNOWN)

(See attachment)

II. BASIS OF JURISDICTION *(PLACE AN "X" IN ONE BOX ONLY)*

- ☐ 1 U.S. Government Plaintiff
- ☑ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES *(PLACE AN "X" IN ONE BOX FOR PLAINTIFF AND ONE BOX FOR DEFENDANT)*
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT *(PLACE AN "X" IN ONE BOX ONLY)*

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury - Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

HABEAS CORPUS:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regulations
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt. Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empt. Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☑ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS - Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce/ICC Rates/etc.
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes
- ☐ 890 Other Statutory Actions

V. ORIGIN *(PLACE AN "X" IN ONE BOX ONLY)*

☑ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION (CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE A BRIEF STATEMENT OF CAUSE. DO NOT CITE JURISDICTIONAL STATUTES UNLESS DIVERSITY.)

This is an action for patent infringement pursuant to 35 U.S.C. § 271(e).

VII. REQUESTED IN COMPLAINT: CHECK IF THIS IS A **CLASS ACTION** ☐ UNDER F.R.C.P. 23

DEMAND $ Declaratory Judgment/Injunctive Relief

CHECK YES only if demanded in complaint: **JURY DEMAND:** ☐ YES ☑ NO

VIII. RELATED CASE(S) IF ANY (See instructions):

JUDGE Freda L. Wolfson	DOCKET NUMBER 03-CV-4179
JUDGE Freda L. Wolfson	DOCKET NUMBER 03-CV-4037
JUDGE Freda L. Wolfson	DOCKET NUMBER 03-CV-5355

DATE
January 20, 2004

SIGNATURE OF ATTORNEY OF RECORD
Jason Halper

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS-44

Authority For Civil Cover Sheet

The JS-44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I. (a) Plaintiffs - Defendants. Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; federal question actions take precedence over diversity cases.)

III. Residence (citizenship) of Principal Parties. This section of the JS-44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. Nature of Suit. Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section IV above, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

V. Origin. Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

VI. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause.

VII. Requested in Complaint. Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. Related Cases. This section of the JS-44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.

CIVIL COVER SHEET ATTACHMENT

PART I(c) (Attorneys; Firm Name, Address and Telephone Number):

Attorneys for Plaintiff:

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973.597.2500
Attorneys for Plaintiffs

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SMITHKLINE BEECHAM PLC, an English Public Limited Company, SB PHARMCO PUERTO RICO INC., a Puerto Rican Corporation, and, SMITHKLINE BEECHAM CORPORATION, a Pennsylvania Corporation, Plaintiffs, v. TEVA PHARMACEUTICAL INDUSTRIES LTD., an Israeli Company, TEVA PHARMACEUTICALS USA, INC., a Delaware Corporation, Defendants.	Civil Action No. _____ **FED. R. CIV. P. 7.1** **DISCLOSURE STATEMENT**

Pursuant to Rule 7.1(a) of the Federal Rules of Civil Procedure, the undersigned hereby certifies that Plaintiffs' parent corporations and any publicly held corporations that own 10% or more of Plaintiffs' stock are as follows:

Plaintiff SmithKline Beecham PLC

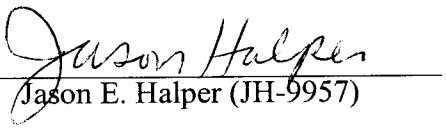
Plaintiff SmithKline Beecham PLC hereby discloses that its parent company is GlaxoSmithKline PLC, and that GlaxoSmithKline PLC is a publicly traded company that owns more than 10% of Plaintiff.

Plaintiff SB Pharmco Puerto Rico Inc.

Plaintiff SB Pharmco Puerto Rico Inc. hereby discloses that its parent companies are: GlaxoSmithKline (Netherlands) B.V., GlaxoSmithKline International (Luxembourg) S.A., Glaxo Wellcome Investments B.V., Glaxo Wellcome International B.V., Glaxo Wellcome Holdings Limited, Glaxo Wellcome Limited and GlaxoSmithKline PLC. GlaxoSmithKline PLC is the only publicly-traded company that owns -- through the aforementioned chain -- 10% or more of SB Pharmco Puerto Rico Inc.

Plaintiff SmithKline Beecham Corporation

Plaintiff SmithKline Beecham Corporation hereby discloses that its parent companies are: GlaxoSmithKline Holdings (Americas) Inc., GlaxoSmithKline Investments (Switzerland) GmbH, Glaxo Wellcome International, GlaxoSmithKline International (Luxembourg) S.A., Glaxo Wellcome Investments B.V., Glaxo Wellcome International B.V., Glaxo Wellcome Holdings Limited, Glaxo Wellcome Limited, and GlaxoSmithKline PLC. GlaxoSmithKline PLC is the only publicly-traded company that owns -- through the aforementioned chain -- 10% or more of SmithKline Beecham Corporation.



Jason E. Halper (JH-9957)

Dated: January 20, 2004